Title

Comprehensive Anaemia Programme and Personalized Therapies (CAPPT): Protocol for a cluster-randomised controlled trial testing the effect women's groups, home counselling and iron supplementation on haemoglobin in pregnancy in southern Nepal

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Short title: Protocol of the Comprehensive Anaemia Programme and Personalized Therapies (CAPPT) trial testing the effect of home visits, tailored iron therapy and women's groups to reduce anaemia in pregnant women in southern Nepal.

Abstract

Background

Anaemia in pregnancy remains prevalent in Nepal and causes severe adverse health outcomes.

Methods

This non-blinded cluster-randomized controlled trial in the plains of Nepal has two study arms: 1) Control: routine antenatal care (ANC); 2) Home visiting, iron supplementation, Participatory Learning and Action (PLA) groups, plus routine ANC.

Participants: Women in 54 non-contiguous clusters (mean 2582; range 1299-4865 population) in Southern Kapilbastu district are eligible if they consent to menstrual monitoring, are resident, married, aged 13-49 years and able to respond to questions. After 1-2 missed menses and a positive pregnancy test, consenting women <20 weeks' gestation, who plan to reside locally for most of the pregnancy, enrol into trial follow-up.

Interventions comprise two home-counselling visits (at 12-21- and 22-26-weeks' gestation) with iron folic acid (IFA) supplement dosage tailored to women's haemoglobin concentration, plus monthly PLA women's group meetings using a dialogical problem-solving approach to engage pregnant women and their families. Home visits and PLA meetings will be facilitated by auxiliary nurse midwives.

Hypothesis: Haemoglobin of women at 30±2 weeks' gestation is ≥0.4 g/dL higher in the intervention arm than in the control. A sample of 842 women (421 per arm, average 15.6 per cluster) will provide 88% power, assuming SD 1.2, ICC 0.09 and CV of cluster size 0.27.

Outcomes are captured at 30±2 weeks gestation. Primary outcome: Haemoglobin concentration (g/dL). Secondary outcomes: Anaemia prevalence (%), mid-upper arm circumference (cm), Mean Probability of micronutrient Adequacy (MPA) and number of ANC visits at a health facility.

Indicators to assess pathways to impact include number of IFA tablets consumed during pregnancy, intake of energy (kcal/d) and dietary iron (mg/d), a score of bioavailability-enhancing behaviours and recall of one nutrition knowledge indicator.

Costs and cost-effectiveness of the intervention will be estimated from a provider perspective.

Using constrained randomisation we allocated clusters to study arms, ensuring similarity with respect to cluster size, ethnicity, religion and distance to a health facility. Analysis is by intention-to-treat at the individual level, using mixed-effects regression.

Discussion: Findings will inform Nepal government policy on approaches to increase adherence to IFA, improve diets and reduce anaemia in pregnancy.

Trial registration: ISRCTN 12272130.

Key Words

Anaemia, pregnant woman, menstrual monitoring, enrolment, haemoglobin, PLA, intervention

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title [1]	Comprehensive Anaemia Programme and Personalized Therapies (CAPPT): Protocol for a cluster-randomised controlled trial testing the effect women's groups, home counselling and iron supplementation on haemoglobin in pregnancy in southern Nepal
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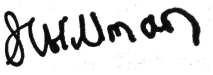
Name and contact information for the trial sponsor [5b]	Health Research and Social Development Forum (HERD) Nepal, PO Box 24133, Prasuti Griha Marg, Thapathali, Kathmandu, Nepal.
Role of sponsor [5c]	The trial sponsor HERD Nepal under the leadership of Sushil Baral, working with the trial coordinating centre, University College London Institute for Women's Health, will take responsibility for all aspects of study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The ultimate authority over these activities is shared between HERD and UCL. The funders have no role in study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Signatory page:

Signatures:

We the undersigned certify that this protocol is a true reflection of the study design of the Comprehensive Anaemia Programme and Personalized Therapies (CAPPT) non-blinded cluster-randomised controlled trial testing the effect upon haemoglobin in pregnancy of participatory learning and action women's groups with home-counselling and tailored iron supplementation compared with standard care in southern Nepal



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Introduction

Background

Anaemia in pregnancy is associated with low birth weight (1-3), perinatal mortality (4) and maternal mortality, with 18% of maternal deaths attributable to severe anaemia (5). A 1 g/dL increase in haemoglobin in late pregnancy can reduce the risk of maternal mortality by 20% (6) cited in (7). Despite government provision of free iron/folic acid (IFA) to pregnant women in many low- and middle-income countries (LMICs), anaemia levels in pregnancy remain alarmingly high (8, 9). The global burden of anaemia in pregnancy is estimated to be as high as 40%(10) and 90% of severe cases are in LMICs, particularly in Africa and South Asia (4, 9, 11, 12).

The aetiology of anaemia is multifactorial (13-15). Dietary iron deficiency is the most common cause of anaemia (12, 13) but other micronutrient deficiencies (1, 16, 17), inherited blood disorders or haemoglobinopathies (sickle cell anaemia and thalassaemia) (18), and parasitic infestations (e.g. malaria and hookworm) (19) are also responsible (12, 15). Iron-deficiency anaemia is estimated to affect 25% (13) to >50% (15, 20) of individuals globally.

In Nepal, estimates of anaemia in pregnant women (PW) vary from 27% according to the 2016 Nepal National Micronutrient Status Survey (NNMSS) (21), to 46% according to the 2016 Nepal DHS survey (22). The burden of anaemia is highest at 52% in the *Terai* (plains) compared to the hills and mountains and varies by season (23), ethnic group, and is higher amongst adolescents, farmers, women of short stature and in women married to illiterate men (24).

The extent to which iron deficiency is driving anaemia in Nepal is difficult to ascertain. The NNMSS found iron deficiency anaemia (IDA) in only 5% of PW (21), but a global review attributed iron deficiency to 55% of the anaemia burden in South Asia (12). Other micronutrient deficiencies in Nepal may also contribute to anaemia (1, 17, 25), although these prevalence estimates also vary widely, at 3-7% for Vitamin A, 28-42% for B12, 12-90% for folate, and 24-90 % for zinc (21, 26-28). This varied and discordant evidence around iron deficiency and anaemia in pregnancy supports the development of a multi-pronged intervention that keeps iron deficiency central but also targets general enhancement of diet and health in pregnancy.

Insufficient dietary intake

Micronutrient deficiencies in Nepalese women are largely attributable to inadequate diets. Although dietary inadequacies have been reported for many micronutrients (29-32), attaining adequate dietary iron intake is particularly challenging (29, 30, 33, 34), especially in pregnancy due to the increased requirements. In the plains of Nepal, the probability of dietary iron adequacy is only 20% and intake of animal-source foods are low (30). Dietary intake is also inequitable, with gender-based discrimination and food restrictions preventing PW from accessing high status, relatively expensive micronutrient-rich foods (31, 35-38). Low awareness of dietary needs in pregnancy (36), food taboos (38) and household power hierarchies (36) may also prevent households from providing micronutrient-rich foods to PW even when they are available. Women may also 'eat down' or eat less than they did before pregnancy for numerous reasons, including; fear of obstructed labour if the baby is large (39), religious fasting, misconceptions about the stomach / intestines 'squashing' the baby, morning sickness (especially in early pregnancy), discomfort or indigestion from eating large meals (40), food aversion and proscriptions such as avoiding foods believed to heat the body (41, 42).

IFA supplementation and antenatal care

A Cochrane review of 44 randomized controlled trials found that iron supplementation during pregnancy reduced the risk of maternal anaemia at term by 70% (43). Accordingly, IFA supplementation in pregnancy has been implemented in many LMICs, including Nepal since 1997. IFA is an integral part of the Government of Nepal (GoN)'s Safe Motherhood programme which also recommends at least four antenatal care (ANC) visits at health facilities at 4, 6, 8 and 9 months of gestation, though recently four additional antenatal 'contacts' with a skilled provider are also being recommended. PW are eligible to receive free IFA from 14 weeks gestation for 180 days of pregnancy and 45 days post-partum from health workers or Female Community Health Volunteers (FCHVs). If a PW is anaemic (<11.0g/dL), GoN recommends the daily IFA dose is doubled from 60 to 120 mg/day (per current WHO guidance (44), though this is not routinely practised. All PW are also advised to take a single dose of 400 mg of Albendazole after the first trimester to reduce the risk of anaemia from hookworm infection (45).

In 2016, Nepal was able to provide some IFA supplementation to 91% of PW, but only 42% completed the minimum 180-day IFA dose. Increasing adherence to IFA could reduce anaemia; a study from the *Terai* found higher odds of anaemia amongst women who took lower doses of IFA ($\leq$143 vs $\geq$144 tablets) (46). To maximise IFA intake, ANC needs to begin earlier in pregnancy (47). In 2016, 31% of PW in Nepal had fewer than 4 ANC visits and 42% of rural women had their first ANC after 4 months (22). In peri-urban breastfeeding Nepalese woman, anaemia appears to have been prevented through IFA supplementation. Women's dietary iron adequacy was 30% and bioavailability of non-haem iron was low due to high levels of phytates in the diet, yet only 5% reported low plasma ferritin iron deficiency anaemia, suggesting that IFA had filled the gap (33). In many places however, supply-side issues may still prevent women from receiving the necessary dose free of cost and some may discontinue IFA consumption due to side-effects (47, 48). Knowledge regarding anaemia, iron deficiency, and IFA supplementation remains low among PW, and improved social support to minimize barriers to uptake and better understanding of the severe implications of anaemia have been suggested as means of improving IFA compliance (47, 49). ANC counselling should discuss benefits of taking IFA, how to manage side effects, how to increase intake and bioavailability of dietary iron and signs of anaemia (44), but time is short for high quality counselling in busy health facilities.

Other drivers of anaemia in Nepal: infections, inflammation and haemoglobinopathies

In addition to inadequate diets and IFA intakes, infections and inflammation are important in the aetiology of anaemia (15, 21). Hookworm infestations are prevalent in Nepalese PW (50, 51) and anaemia prevalence was higher amongst PW who had not consumed deworming medication in the past six months compared to those who had (21), highlighting the importance of quality ANC to detect and treat infections.

Iron metabolism is influenced by haemoglobinopathies (15, 52) and by genetic variation in individuals' ability to absorb iron (53). The NNMSS tested NPW for blood disorders and found 1% had alpha-thalassemia, 3% beta-thalassemia, 1% sickle cell and 14% glucose-6-phosphate dehydrogenase deficiency (21). These haemoglobinopathies, which account for 12% of female anaemias worldwide (11) and are associated with low haemoglobin during pregnancy (54), are usually not amenable to iron treatment and may limit the effectiveness of IFA supplementation (15) in a small proportion of cases.

A combined approach of improving diets, increasing IFA uptake and tailored dosage according to guidelines, and reducing infection could be an efficient way of tackling anaemia in Nepal, especially in *Terai* populations where anaemia prevalence is high.

Potential interventions to improve anaemia in Nepal

With IFA supplementation routinely provided in many LMICs yet anaemia remaining stubbornly prevalent, effective behaviour-change interventions in pregnancy are needed to increase IFA compliance, enhance dietary micronutrient intake and bioavailability, and reduce infections/inflammation through deworming (44).

Home visiting counselling and nutrition education approaches have shown promise. In India, a home visiting nutritional counselling model for PW reduced anaemia from 96% to 79% and improved Hb by >1g/dL (55). In Nepal, an education program with routine iron supplementation improved haemoglobin levels in PW by up to 0.26 g/dL and reduced anaemia prevalence by 65% (56). However, a systematic review of nutrition education and counselling (NEC) interventions found that effects are highly variable. When combined with provision of food or supplements, women's risk of anaemia in late pregnancy was reduced by 42%, but without this NEC effects were smaller (16% lower risk) and only marginally significant (57). In situations or environments that are not enabling, educating women and families may not automatically provoke changes in behaviour. A long literature on behaviour change theory (58-60) and qualitative research (36) indicates that nutrition education may need to be coupled with additional components that address wider contextual factors that enable women and families to implement new knowledge. As indicated by the NEC review, this includes access to food and supplements. Other studies, including our formative research, suggest this also includes addressing complex factors such as gender norms, power hierarchies, community cohesion, and trust in health services (61).

To address some of these wider community-level factors, women's groups may be an effective intervention, but as with NEC, a review of 36 studies on the effects of women's groups found highly heterogeneous effects on nutrient intakes (62). This heterogeneity may be due to differences implementation, context, or ways the intervention interacts with context. Researchers have suggested a typology of women's groups to help identify differences in approach: classrooms (didactic behaviour

187 change), clubs (build relationships between members), and collectives (engage the whole community) (63).
188 In the case of anaemia, a 'collective' approach may be needed. One form of collective approach uses
189 Participatory Learning and Action (PLA), which follows a four phase 'cycle' of problem identification,
190 planning strategies to overcome the problems, implementing the strategies and evaluating them. The PLA
191 approach is based on the theory that many health problems are rooted in powerlessness and may be
192 addressed by social and political empowerment (64-66). Hypothesised pathways to impact include women
193 sharing experiences and motivating each other to try new behaviours, collective ownership of nutrition
194 problems, increasing resources to afford better nutrition, and changing social norms to promote healthy
195 behaviours. Several interventions using PLA groups in South Asia have been highly effective at improving
196 health outcomes, particularly reducing maternal and neonatal mortality (67-73) and diabetes (74).
197 However, effects on women's diets and anthropometry have been less consistent, showing small (75),
198 mixed (76-78) and sometimes null effects (74). The only study that has reported effects of PLA on
199 haemoglobin is the UPAVAN trial in India which combined PLA with an agricultural intervention (79), which
200 showed no impact on mothers' haemoglobin or MUAC but did improve dietary diversity (80).
201 **CAPPT rationale**
202 Taken together, evidence demonstrates that anaemia could be reduced in rural Nepal by (1) increasing
203 adherence to WHO recommendations on IFA (tailoring dose according to anaemia status and increasing
204 PW's compliance), (2) improving diets to increase intakes of iron, bioavailability of iron, and other
205 micronutrients, and (3) increasing access to deworming tablets. Previous trials suggest that both PLA and
206 NEC could improve diets and haemoglobin concentrations, but evidence of their effectiveness when
207 integrated has not been studied. Hence, CAPPT will test an intervention to reduce anaemia by addressing
208 IFA, diets and deworming, using a combined approach of PLA groups with two nutrition counselling home
209 visits to PW at home in a disadvantaged population in the Nepal *Terai*.
210 The CARING trial in India showed that a single home visit to third trimester pregnant women, combined
211 with PLA groups, improved PW's dietary diversity but not MUAC (76), so our model of two home-based
212 counselling visits in early to mid-pregnancy combined with PLA groups could also improve diets. Experience
213 from the Low Birth Weight South Asia Trial (LBWSAT) in the *Terai* showed that: PLA groups wanted to

implement home visits as part of their strategies (77); women may be unable to leave the home in pregnancy, especially during their first pregnancy (81); and PLA group attendance by pregnant women was a higher when PLA was combined with cash or food transfers (77). Home visits might work synergistically to encourage PLA group attendance, reach women who cannot / do not leave their homes, and engage household members who oversee food purchasing and allocation decisions (males and mothers-in-law) (36). We hypothesise that our planned home visiting intervention will facilitate personalised, direct one-to-one support to PW and their families, while the PLA groups will work at the community-level to create an enabling environment, changing community-level norms, and facilitate shared exchange of nutrition knowledge and peer support among group members.

Objectives [7]

7. Specific objectives or hypotheses

The primary objective of the Comprehensive Anaemia Programme and Personalized Therapies (CAPPT) trial is to assess the impact on haemoglobin (Hb) at 30±2 weeks of pregnancy, of an integrated intervention providing personalized nutrition counselling at pregnant women's homes, together with tailored dosage of oral iron-folic acid (IFA) and PLA women's groups in the community, in addition to routine ANC, compared with a control arm where women have access to routine ANC only.

Secondary objectives are as follows:

1. Assess the impact at 30±2 weeks gestation of this integrated intervention by comparing prevalence of anaemia, mean probability of adequacy (MPA) of 11 micronutrients, mid-upper arm circumference (MUAC) between study arms and count of ANC visits at a health facility.
2. Explore potential pathways to impact by comparing between study arms: count of IFA supplements consumed; daily energy and iron intakes, behaviours to enhance bioavailability, nutrition knowledge.
3. Compare intervention effects between population subgroups such as wealth groups, baseline BMI category and anaemia levels.

4. Undertake a dose-response analysis to analyse the effect of different levels of exposure to PLA groups, home visits and number of IFA consumed, separately and in combination
5. Conduct a process evaluation to describe exposure, implementation, and fidelity of the intervention to that planned and measure hypothesised changes in target behaviours of pregnant women and their families including bargaining power and decision-making power, equity of food and nutrient allocation between PW and their husbands, experience of side effects of iron therapy, health literacy.
6. Estimate cost and cost-effectiveness of the intervention package from a provider perspective.

Trial design [8]

This is a non-blinded parallel group two-arm cluster-randomised controlled trial, with an allocation ratio of 1:1, conducted in Kapilbastu district in the rural plains of Nepal. Trial arms are: 1) control (routine antenatal care (ANC); 2) 'Home visiting plus PLA' intervention package comprising a combination of tailored IFA supplementation and counselling at home, and Participatory Learning and Action (PLA) meetings held in the community, in addition to routine ANC.

Methods: Participants, interventions, and outcomes

Our study protocol follows SPIRIT guidelines (82) as outlined in a SPIRIT checklist provided in Supplementary Annex 1.

Study setting [9]

The study is set in Kapilbastu district in Province 5 in the Western *Terai* (plains) of Nepal, bordering Uttar Pradesh state of India. The district population is 569,844 with an estimated crude birth rate of 21.3 per thousand population per year (83). The population comprises predominantly *Madhesi* (plains) ethnicity Hindus with sizable minorities of disadvantaged Muslims and Dalits. Literacy rates are 45% and 65% amongst women and men respectively (83). The lowland area is characterised by rice production with winter crops of wheat and pulses, with high temperatures and humidity for much of the year. Kapilbastu's

Human Development Index is 0.452, putting it in the second-least developed category of districts in Nepal (84). Anaemia in women of reproductive age was 44% in 2016 (22).

Eligibility criteria [10]

Cluster selection

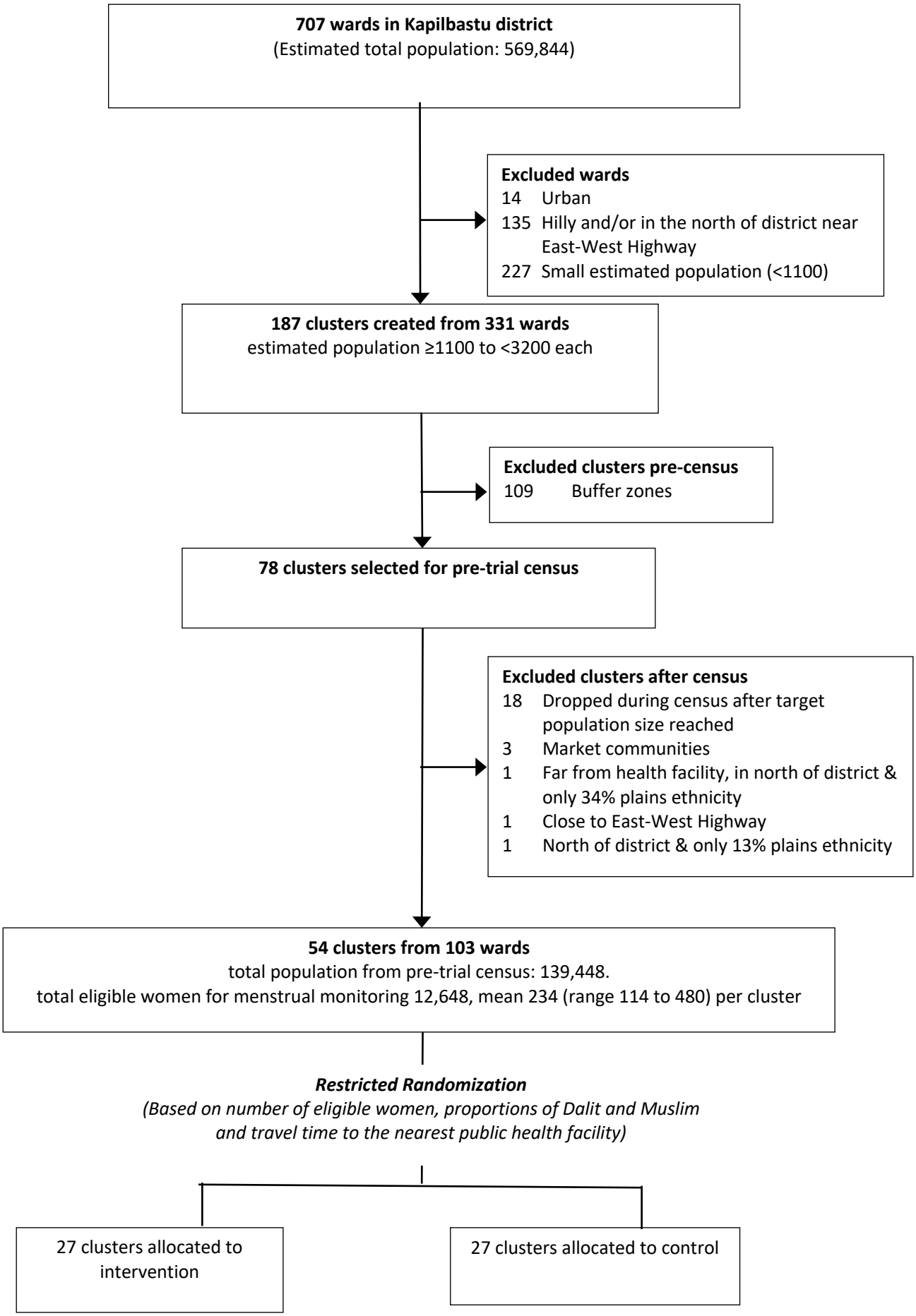
Prior to federal restructuring in 2017, the smallest geopolitical unit of administration in Nepal was the Village Development Committee (VDC), each divided into nine wards (hereafter 'old wards'). Each old ward forms the catchment area of one Female Community Health Volunteer (FCHV) who is responsible for holding monthly health mothers' group meetings in the community. Since these groups are the platform for our PLA intervention, we chose old wards as the basis for forming study clusters.

We estimated cluster population by applying World Bank annual population growth rates (85, 86) to Kapilbastu 2011 census data at the old-ward level (83). On the basis of pregnancy detection rates in LBWSAT data, we predicted that 2.52 pregnancies/1000 total population could be detected per month per ward and conservatively assumed that up to two-thirds of the pregnancies detected would be >20 weeks' gestation, which would be too late to enrol into the trial.

Cluster inclusion criteria were set to ensure that the majority of participants will be from the population group with the highest anaemia prevalence in the district, which is Madhesi ethnicity rural women who make up the majority of the community in the south of Kapilbastu district. Hence our cluster inclusion criteria are not adjoining the main East-West highway that traverses Nepal; lying in the southern part of Kapilbastu district (closer to the Indian border) where there is less population heterogeneity and lower forest coverage; in a rural area with no major market; projected population of ≥1100 and <3200 from Nepal 2001 census; surrounded with a buffer zone of non-study clusters; and >50% Madhesi (plains ethnicity) as per the pre-trial census (below).

Figure 1 summarises the process of excluding old wards on the basis of population size and location within the district, merging them to come up with a sample of 78 clusters eligible for inclusion in the pre-trial population census, and exclusion of cluster post-census.

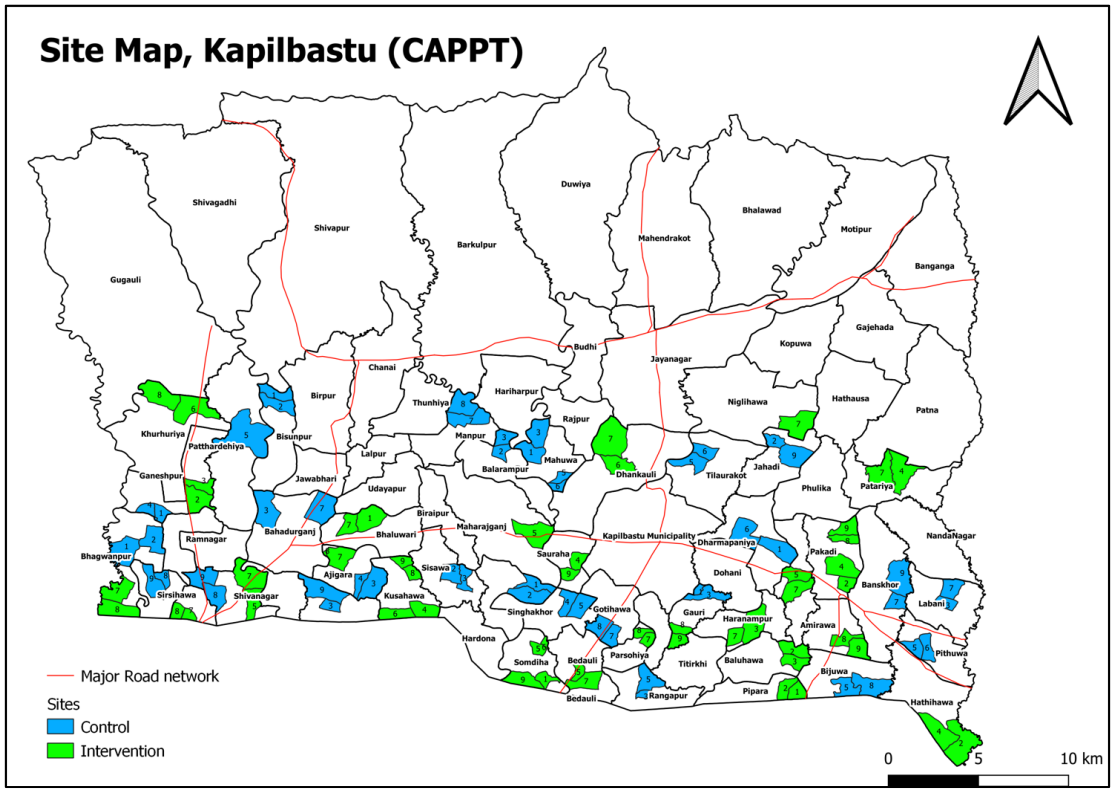
Figure 1. Flowchart of the process of study cluster selection



Pre-trial census

From November 2019 to February 2020, we conducted a census to quantify the number of married women of reproductive age and describe cluster characteristics that could be used in restricted randomisation to allocate clusters to study arms such as caste, religion, household size, education, and distance to the nearest public health facility. Although we originally planned to include all 78 eligible clusters, we decided to halt data collection after 60 clusters had been completed, since the population per cluster was considerably higher than predicted, dropping the 18 remaining clusters. The higher population per cluster also meant we needed only 54 clusters for the trial. Of the 60 clusters included in the census, we found that 6 were atypical on the basis of having a high proportion of hills ethnicity, being close to the east-west highway, far from the nearest public health facility or having a dense population with busy marketplace. Consequently, we dropped these clusters, resulting in the final selection of 54 clusters comprising 103 old-wards (5 single- and 49 merged pairs of- old-wards), which have been randomly allocated to 27 clusters per arm, are listed in Supplementary Annex 2 and mapped in Figure 2. The total population enumerated in the census is 139,448, mean 2582 (range 1299-4865) per cluster. The population of women identified as eligible for menstrual monitoring in the census is 12,648, mean 234 (range 114 to 480) eligible women per cluster.

Figure 2. Map of study clusters showing randomly allocated clusters



Individual Participant eligibility

Inclusion criteria to be enrolled into menstrual monitoring (to detect pregnancy) are being a married woman between the ages of 13 and 49 years: being resident in the study cluster (whether at her husband's or parental home); could become pregnant (i.e., she and her husband have not had permanent sterilization such as tubal ligation or vasectomy, has not attained menopause nor had a hysterectomy); and consents to being asked about their menstrual status once every four weeks.

Inclusion criteria for a woman to be enrolled into trial follow-up include: a married female aged 13 to 49 years with a positive pregnancy test, at less than 20 weeks' gestation, who is able to provide informed consent/assent and respond to survey questions. The gestational age is estimated from the date of the last menstrual period (LMP) as recalled by the PW, which is cross-checked against LMP dates recorded in the menstrual monitoring register during menstrual monitoring. If a PW has already visited a health facility for an ultrasound test, this report is also checked before enrolling the woman.

Exclusion criteria include non-consent and/or unable to respond to questions, ≥20 weeks' gestation from LMP (or uterus clearly visible above the level of the umbilicus if LMP is not recalled / not available), and not planning to reside in the study cluster for most of her pregnancy.

Although the study participants give consent, their family members are also encouraged to participate in home visits and women's groups. We will also ask for consent from husbands or adult male household members (or mother-in-law if no adult male), to measure their diets in addition to the PW.

Who will take informed consent? [26a]

Letters of approval to work in selected clusters were received from municipality officials by field managers employed by HERD International before undertaking the census. Household heads provided written / thumbprint consent to collect census data.

All consent for individual participation (using signature or thumbprint) is taken by interviewers at the beginning of menstrual monitoring and again at enrolment into follow-up when pregnancy is detected. After obtaining written consent, interviewers take oral consent at subsequent menstrual monitoring and trial follow-up visits. A participant is free to withdraw consent or refuse data collection on any of these

occasions. Interviewers will take written consent from the married woman herself where she is 18 years or above. For adolescents 13 to 17 years, interviewers will take written consent from guardians and written assent from the adolescent, and both shall be required for the girl to participate. Supplementary annexes 3 to 6 provide the trial participation information sheets and consent forms in English (copies in Nepali and Awadhi available on request).

Additional consent provisions for collection and use of participant data [26b]

Every consent form has a clause asking permission to share the anonymised data collected in this study with other researchers to conduct secondary analyses and to revisit the participant for future follow-up studies, should the need arise.

Formative phase

Policy engagement

We interacted with government stakeholders at federal, provincial, and local levels, meeting with Ministry of Health & Population and Family Welfare Division, Province 5 Ministry of Social Development and Provincial Health Directorate, Kapilbastu Health Office, and elected municipality representatives. We orientated stakeholders about, and received their support for, trial activities around the time of the census, and whilst randomly allocating clusters to study arms. Before starting the interventions, we will orientate the municipal health team, health workers and FCHVs in selected clusters.

Formative research

We conducted a scoping review of literature to identify the current anaemia burden in PW, their dietary practices, health-seeking behaviour, and research gaps for Nepal and South Asia. To explore the factors affecting compliance and consumption of IFA, access to antenatal care, and consumption of micronutrient rich food we conducted a detailed qualitative study in two rural and one urban municipality of Kapilbastu. We analysed pre-existing dietary data from LBWSAT in Nepal using 'Optifoods' linear programming software (87) to draw up dietary recommendations on the basis of available foods. The Optifoods analysis confirmed the difficulty in achieving an iron-replete diet using locally available foods, especially amongst vegetarians, but was helpful in identifying some key iron-rich foods to promote.

Interventions

Explanation for the choice of comparators [6b]

We compare intervention with control clusters, where women do not receive the interventions but have access to routine antenatal care services within the government health system. Menstrual monitoring in both intervention and control clusters may mean pregnancies are detected earlier, and women may receive ANC and/or IFA earlier, than outside the study area.

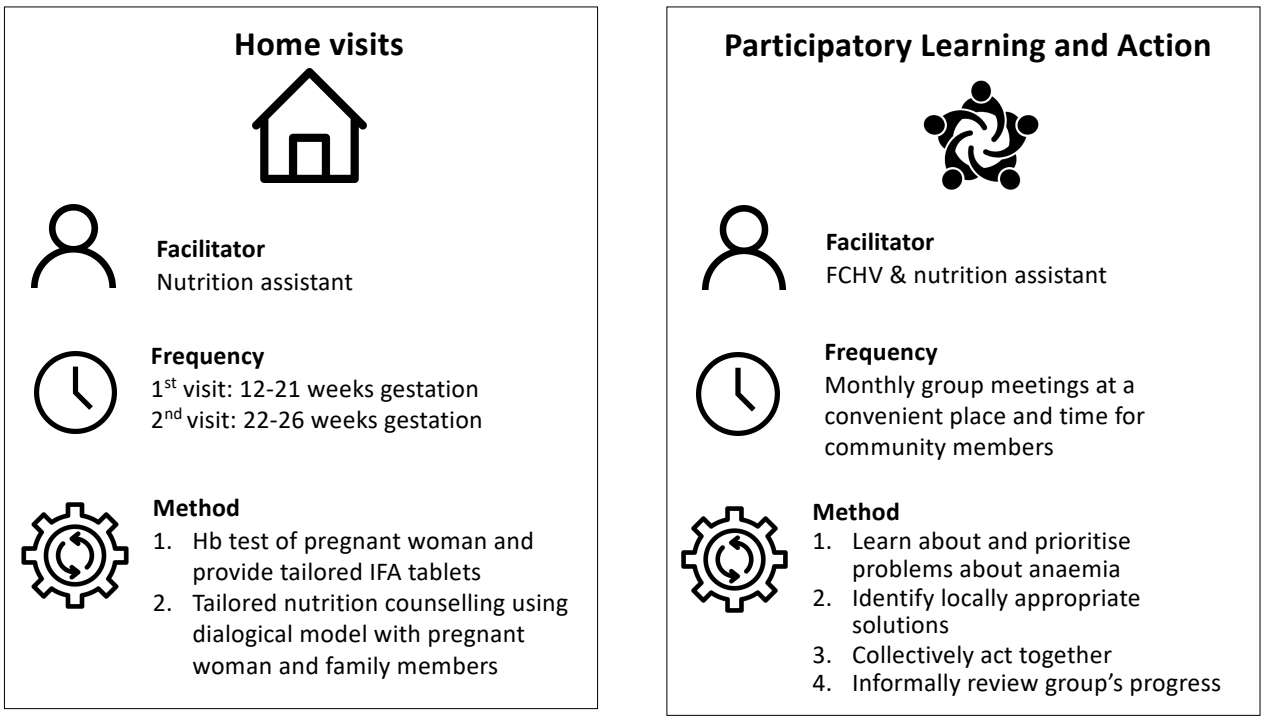
Intervention description [11a]

Intervention staff recruitment and training

Six certified auxiliary nurse midwives are employed by HERD as Nutrition Assistants (NAs) to deliver tailored home visits to PW and facilitate PLA women's groups in 4-5 intervention clusters each. Training of NAs will involve role-play practice sessions and field testing of intervention activities. Topics include: i) health consequences of anaemia in pregnancy and anaemia prevention / treatment; ii) diet in pregnancy and how to increase iron intake and bioavailability; iii) communication skills; iv) how to engage families in dialogue and problem solving; iv) use of Hemocue to measure Hb levels; v) use of mobile phones/tablets and CommCare for recording and reporting of intervention activities; vi) how to run women's groups following a PLA intervention manual.

A diagram summarising the home visiting and PLA interventions is shown in **Figure 3**.

Figure 3: Components of the combined home visiting and Participatory Learning and action (PLA) interventions



Home visiting intervention:

Home visits are designed to work synergistically to encourage PLA group attendance, to reach women who cannot / do not leave their homes, and to engage family members. Each home visit will comprise dialogical counselling, home-based anaemia screening, and tailored provision of IFA. The NA will visit each PW twice at home, first at 12 to 21 weeks and second at 22 to 26 weeks. Ideally the gap between visits will be 4 to 6 weeks, unless logistical constraints imposed by the COVID-19 pandemic disrupt activities.

Home-based tailored dialogical counselling

We will take a *dialogical* approach to engage pregnant women and their families to think critically about the causes of anaemia in pregnancy in their household and community. The NA will engage pregnant women and their families in a cycle of action and reflection: 1) listening for the key issues and emotional concerns of the household; 2) promoting participatory dialogue about these concerns; and 3) planning and taking action about the concerns that are discussed. At the first and second home visits, the NA will use stories and inductive questioning to trigger dialogue and reflection (66). Stories will directly address issues from our formative research. We will train the NA about common issues that may arise and provide a

discussion and reference manual with examples of actions that pregnant women and their families could take. Families will make specific action plans to address the issues that are relevant for their family and in the second visit these will be reviewed, and a different story used to trigger discussion and reflection. The tailored counselling aims to support women and their families to take actions to change dietary practices, take IFA and deworming tablets, attend PLA groups, and access antenatal care. If the NA observes any pregnancy danger signs, as per the government's standard treatment protocol (45) she will advise the woman to seek care straight away from the nearest appropriate health facility.

Anaemia screening and tailored iron-folic acid therapy

At each home visit, following the nutrition counselling, the NA will measure the PW's haemoglobin concentration using a hand-held Hemocue Hb 301+ analyser, measure her mid-upper arm circumference (MUAC) with a SECA tape (93/42/EEC) to assess thinness, and explain the results. Following GoN guidelines, the NA will advise the PW to take IFA as follows:

- Not anaemic (Hb≥=11 g/dL) one IFA tablet (60 mg elemental iron and 400 μg folic acid) per day.
- Mildly or moderately anaemic (Hb 7-10.9 g/dL) two IFA tablets (120 mg elemental iron and 800 μg folic acid) per day.
- Severely anaemic (Hb < 7 g/dL) the NA will immediately refer the PW for a blood transfusion at a higher health facility.

At visit 1 (at 12 to 21 weeks' gestation) the NA will provide sufficient IFA tablets for a period of 4-10 weeks until her second visit, at 22 to 26 weeks' gestation. For all women, NAs will emphasise the importance of increasing dietary diversity and consuming micronutrient-rich food. For women with low (<230 mm) or very low (<210 mm) MUAC, the NA will also emphasize the importance of consuming additional calories through more frequent and/or larger meals and taking adequate rest. For women with MUAC ≥300mm, the NA will stress the importance of keeping active during pregnancy and avoiding sugary or fatty foods and large portions of rice.

After repeating the haemoglobin and MUAC measurements at the second visit, the NA will explain to the woman how her anaemia and thinness status have changed and provide the appropriate IFA dose. She will also assess compliance to IFA by asking the PW about their tablet consumption and checking used blister

446 packs. At visit 2, the NA will provide a single (400 mg) albendazole tablet if the PW has not already received
447 it as per Nepal's national protocol for women in their second trimester.
448 The NA will record details of haemoglobin and MUAC readings, IFA and albendazole tablets provided on the
449 Trial Participation Card (TPC) at each visit to enable participants to show health workers what treatment
450 they have been receiving. The NAs will make two copies of discussion action sheets to record actions
451 agreed to reduce anaemia based on the issues identified. One copy will be given to PWs family, and the
452 other copy will be kept by the NA for reference. The NA will also record Hb, MUAC, IFA and albendazole
453 given, and the actions agreed upon with the PW's family on an electronic data collection form just after the
454 visit is concluded. The NA will not enter data on the tablet or phone during the visit to allow fluid
455 interpersonal interaction but will take a photograph of the TPC and the discussion action sheet before
456 leaving the home.
457 The modality of the home visiting intervention is shown in **Figure 4**.
458

459 **Figure 4: Modality of the home visiting intervention**

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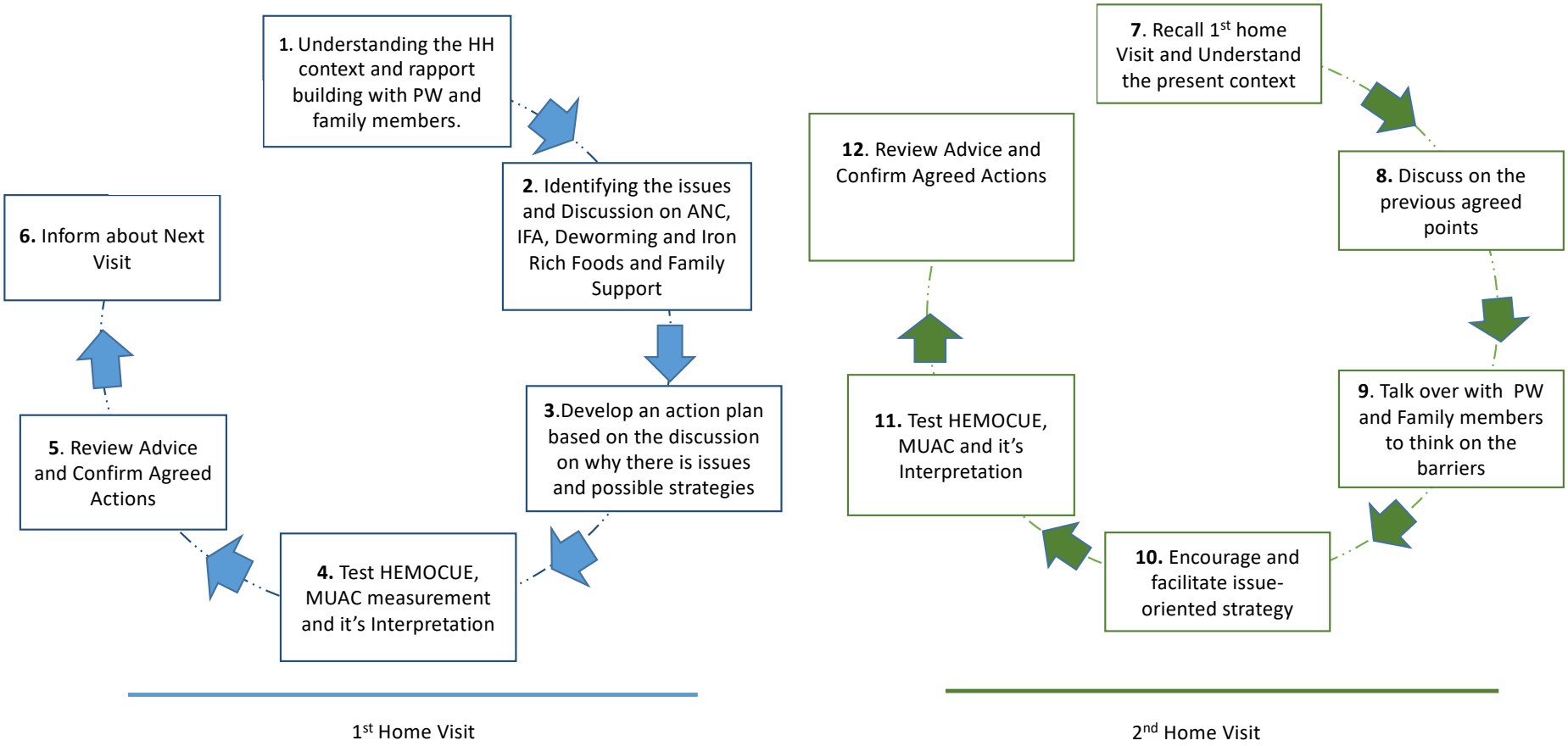
461



Participatory learning and action women's group (PLA) intervention

In the intervention arm, the NA, together with the local FCHV for that cluster, will facilitate monthly groups at a convenient place and time for community members. As FCHVs are mandated by the health system to hold monthly mothers' groups, we will work through these groups where they already exist and revitalise them where they are inactive.

The groups will run for a 15-month period, from the last month of menstrual monitoring consent to (about one month before the first enrolment) until after the last enrolled woman has completed 30±2 weeks gestation. NAs, who are locally recruited and trained, will train the FCHVs on the PLA meeting manual each month and the FCHVs will assist the NAs in group facilitation. Groups are open to anyone who is interested, and participation is voluntary. As restrictive gender norms can prevent women's participation in mixed groups, the first 10 meetings will be exclusive to women. Men will be invited to a large community planning meeting and groups will discuss how they would like to engage with men thereafter.

The PLA cycle will consist of four phases 1) problem identification, 2) planning together, 3) strategy implementation and 4) strategy evaluation. During the 'problem identification' phase, over 6 monthly meetings, groups are introduced to the PLA method, discuss local definitions and beliefs about the causes and symptoms of anaemia, and local beliefs around taking IFA supplements. They will then discuss barriers to good nutrition to improve anaemia, and barriers to uptake of IFA supplementation during pregnancy. During the 'planning together' phase, over 3 monthly meetings groups prioritise problems that they would like to address and plan and implement a community meeting to engage the wider community. Groups will then lead on the implementation of these strategies in Phase 3 and will continue discussing new topics related to anaemia in pregnancy. They will evaluate the effect of their actions in Phase 4 by reflecting on the original problems and progress in solving them. Then they may reformulate strategies to begin another phase of implementation.

During the PLA cycle, facilitators use a pictorial meeting manual which contains varied triggers for discussion – such as a story, a quiz, or game – which are often used with picture cards. These focus on iron-rich foods and how to increase bioavailability, improve IFA compliance, reduce side effects, and manage nausea and minor pregnancy ailments, and when to seek care for more serious problems.

Criteria for discontinuing or modifying allocated interventions [11b]

We do not expect that the tailored counselling or PLA women's groups to have any negative effects upon trial participants, but some women may experience side-effects from consuming IFA or from deworming. Side-effects commonly experienced from IFA include constipation and indigestion (1, 88) but these tend not to be serious. Recent studies have also indicated that iron supplementation may increase susceptibility to infections but that this is more common in children than adults (89). Interviewers will collect data on side effects of IFA and on morbidity of women during the 30±2-week interviews and NAs will ask women about side effects and advise how to mitigate them during counselling sessions and at women's groups. In exceptional cases, if the higher IFA dose is not being tolerated, the NA may advise the woman to reduce intake from two to one tablet per day. All women who are feeling unwell at the time of interaction with the NA or data collector are advised to seek care at their nearby health facility or at a higher care centre where needed.

Strategies to improve adherence to interventions [11c]

Nepal's national protocol is to provide PW with IFA from 20 weeks' gestation onwards till 45 days post-partum from all health facilities, outreach clinics and FCHVs. Doubling the dose for anaemic women is in the GoN protocol but usually not practised. We will orient all health workers at the health facilities in/near intervention areas, and the district and regional hospitals, about the intervention and the distribution of IFA and albendazole tablets by the NA during home visits and encourage them to practice administration of double dose for women who have been identified as anaemic in line with NA prescription. NAs will ask women to show their home-visit TPC records of Hb, MUAC, IFA and albendazole tablets to health workers at the beginning of each ANC consultation to ensure women are not prescribed double doses of IFA or albendazole. The NAs will visit health facilities every month and provide a list of the enrolled participants and the number of tablets provided to them to avoid duplication. For more distant health facilities, or where visiting health facilities is restricted by COVID-19, information is sent by email or SMS and NAs phone health workers to ensure the information has been received.

NAs attend monthly meetings with intervention coordinators to reflect on the previous PLA meeting and plan for the next. Through discussion and role-play, facilitators develop common methods of holding meetings. While the trial surveillance system is getting established, a one-month 'run-in' of women's groups allows time for groups to get established before the first 'full-trial' PW enrols. The picture cards and women's group manual can be modified as needed to ensure that content is realistic, understandable, culturally appropriate, visually appealing, and motivating, but any changes will be applied across all intervention clusters.

Relevant concomitant care permitted or prohibited during the trial [11d]

Women who receive home-visits and tailored doses of IFA and deworming are strongly discouraged from taking additional doses of micronutrients or additional deworming. NAs and interviewers encourage PW to seek concomitant care for any illnesses they may be experiencing which are reported during interactions. If the interviewer or NA detects severe anaemia, they give the PW a referral slip, and advise her to go immediately to the district hospital or other referral centre where transfusions are available.

Provisions for post-trial care [30]

We do not envisage complications that would require compensation but have necessary insurance arrangements in place.

Outcomes [12]

All outcomes are measured during 30±2-week interviews and are listed in Table 1 below.

The primary outcome of the trial is mean haemoglobin concentration in g/dL ascertained from a Hemocue 301+ analyser reading. Secondary outcomes are prevalence of anaemia (% Hb< 11.0 g/dL), mid-upper arm circumference (cm), and mean Probability of Micronutrient Adequacy of 11 micronutrients including vitamin A, riboflavin (B_2), niacin (B_3), pyridoxine (B_6), cobalamin (B_{12}), thiamine (B_1), folate (B_9), vitamin C, iron, zinc, and calcium.

Indicators to compare between arms to assess pathways to impact include: count of ANC visits at a health facility, number of IFA tablets consumed during pregnancy, intakes of energy (kcal/d) and dietary iron excluding supplements (mg/d), a score of bioavailability enhancing behaviours (comprised of: avoiding tea and coffee at or near mealtimes, use of vitamin C-rich foods with food and IFA tablets, use of sprouted pulses or grains, and spreading of haem-iron foods over 2 eating occasions), recall of nutrition knowledge indicators pertaining to iron-rich foods, importance of IFA, and ways to improve bioavailability of iron.

Table 1: Trial outcomes and indicators on the impact pathway

CAPPT TRIAL OUTCOMES	Effect measure to compare arms / summary statistic
Primary outcome at 30±2 weeks	
Haemoglobin concentration ascertained from a Hemocue 301+ analyser reading (Hb g/dL)	Difference /Mean
Secondary outcomes at 30±2 weeks	
Prevalence of anaemia (% Hb< 11.0 g/dL)	Odds Ratio/Proportion
Mid-upper arm circumference (cm)	Difference /Mean
Mean Probability of Adequacy (MPA) of 11 micronutrients including vitamin A, riboflavin (B_2), niacin (B_3), pyridoxine (B_6), cobalamin (B_{12}), thiamine (B_1), folate (B_9), vitamin C, iron, zinc, and calcium;	Difference / Mean
Total number of ANC visits a health facility	Ratio / Mean
Indicators on the pathway to impact to be compared between arms at 30±2 weeks	
IFA tablets consumed by time of measurement at 30±2 weeks	Ratio / Mean
Usual energy intake (kcal/d)	Difference /Mean
Usual dietary iron intake (excluding supplements) (mg/d)	Difference /Mean
Uptake of methods used to improve bioavailability	Ratio / Mean
Nutrition knowledge score	Ratio / Count

To describe intervention implementation and potential mechanisms by which the intervention and its components may have an effect, we also collect process outcomes given in Table 2. Exposure to PLA groups, number of home visits, and side effects will be reported in the main trial paper, together with factors which emerge as key indicators of intervention fidelity. Other process indicators may be reported in one or more separate publications Process indicators include weight gain in pregnancy, gestational age at first ANC, amounts of promoted foods consumed, health literacy, social networks, and social norms. For assessment of the effect of the intervention upon intra-household food allocation we measure ratios of MPA, energy adequacy and iron intake between the PW and her husband (or senior household member).

For the purposes of tracking any potential harms we track side effects from taking IFA tablets including vomiting, constipation and indigestion or heart burn and report them to the DMC.

Table 2: Process indicators

Intervention exposure and activities
Number of home visits received (0, 1 or 2)[1]
Family actions agreed upon in the home visit
Which family members took part in the home visit interaction
Doses of IFA prescribed
Exposure to PLA community strategies[1]
Whether any family members attended PLA groups
Which family members attended
Social and behaviour change processes
Health literacy
Social norms
IFA and ANC processes
Numbers of IFA tablets consumed in relation to those prescribed
Uptake of any antenatal care
Quality of antenatal care
Gestational age at first ANC visit
Dietary processes
Amounts of key promoted foods consumed by pregnant women
Intra-household allocation, as PW's share [PW / (PW + senior male)] of nutrients in term of Mean Probability of Micronutrient Adequacy, iron intake, and energy adequacy
Weight gain in pregnancy from enrolment to 30±2 weeks (kg)
Side effects
Constipation[1]
Indigestion / heart burn[1]
Vomiting[1]

[1] These process indicators will be reported in the main trial paper whereas others may be reported in one or more separate process evaluation publications rather than in the trial paper

Participant timeline [13]

Formative work ran from May 2019 to February 2020 but trial roll-out was delayed because of the Novel SARS-CoV-2 Corona Virus (COVID-19) pandemic which began to affect Nepal in March 2020, just as trial enrolment was due to begin. Since census data is now out of date, several months of formal menstrual monitoring consent-taking and updating the census with new women or households is required before enrolment can begin. The trial timeline from when we are able to start the trial, showing the schedule of enrolment, interventions and assessments (as per the SPIRIT figure guidelines), is provided in **Figure 5.** Data

collectors will enrol women for one run-in and six full-trial months and follow-up every woman until the last enrolled woman reaches 30±2 weeks. The 'full trial' phase will last for 14 months and only women recruited after the run-in month will be included in the final analysis.

576 **Figure 5. Schedule of enrolment, interventions and assessments (SPIRIT Figure)**

577

Month																					
Schedule of enrolment, interventions, and assessments	**pre-trial**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
FORMATIVE RESEARCH																					
Pre-trial qualitative study and formulation of dietary recommendations using Optifoods	1																				
Market survey for food availability and price		1																			
Formative work to develop and refine food list, collect standard recipes, pilot portion size food models, collect seasonal calendars of food availability and refine mobile app		1	2	3	4																
ALLOCATION																					
Random allocation of 27 clusters to each arm, constrained on the basis of cluster size, ethnicity, religion and distance to nearest health facility	1																				
ENROLMENT (54 clusters)																					
Pre-trial census to detect eligible women	1																				
Taking informed **consent for Menstrual Monitoring** from eligible women		1	2	3	4																
Menstrual monitoring (1 month run in, 6 month full trial) to detect pregnancies						1	2	3	4	5	6	7									
Taking informed consent to **enrol pregnant women** <20 weeks gestation						1	2	3	4	5	6	7									
INTERVENTIONS (27 clusters)																					
Participatory Learning and Action (PLA) women's groups for pregnant women, their families and community members					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
Home counselling visit 1 at 12 to 21 weeks' gestation (with recording of haemoglobin (Hb), mid-upper arm circumference (MUAC) and discussion and actions agreed)						1	2	3	4	5	6	7	8	9	10	11					
Home counselling visit 2 at 22 to 26 weeks' gestatiopn (with recording of Hb, MUAC, discussion and actions agreed)							1	2	3	4	5	6	7	8	9	10	11				
ASSESSMENTS (54 clusters)																					
Baseline data collection from pregnant women <20 weeks gestation: haemoglobin measured with Hemocue 301+ analyser (Hb), anthropometry (weight, height, body mass index (BMI), mid-upper arm circumference (MUAC)), exposure to early antenatal care (ANC), intake of iron folic acid (IFA), socioeconomic and demographic indicators (assets, household characteristics, sanitation, food security, education)						1	2	3	4	5	6	7									
30+/-2 weeks' gestation endline data collection: Hb, anthropometry, uptake and quality of ANC, intake of IFA, side effects of IFA, morbidity, uptake of methods to improve bioavailability, health literacy, social norms, exposure to interventions (home visits and PLA groups).								1	2	3	4	5	6	7	8	9	10	11			
Quantitative 24-hour dietary recalls at 28-32 weeks gestation (duplicates 2-7 days apart) of pregnant woman and her husband (or senior male household member) to obtain: Mean Probability of Adequacy of 11 micronutrients, intakes of energy, iron, promoted foods, Intra-household allocation, as PW's share [PW / (PW + senior male)] of nutrients in term of Mean Probability of Micronutrient Adequacy, iron intake, and energy adequacy.								1	2	3	4	5	6	7	8	9	10	11			

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Legend:

Pre-trial census and cluster allocation	
Menstrual monitoring	
Run-in	
Intervention	
Surveillance of pregnant women in trial	
Dietary component activities	

Sample size [14]

Our trial includes 54 clusters with 6 months of enrolment. We assume 2.52 pregnancies will be detected per month per 1000 population, based on the rate observed in LBWSAT, which used a similar pregnancy detection mechanism. For women to be recruited, their pregnancy must be detected at <20 weeks' gestation. In LBWSAT, 55% of the pregnancies detected were <20 weeks' gestation at enrolment. So, for our sample size calculations we assumed a best-case scenario of 50% and a worst case of 33% detected pregnancies <20 weeks. We assume 20% loss to follow-up from enrolment to measurement of the primary outcome at 30±2 weeks gestation, including losses due to miscarriage or termination and women migrating to their parental homes during pregnancy. Therefore, for the best-, and worst- case enrolment scenarios we expect an average of 15.6 and 10.4 primary outcome measures achieved per cluster respectively, giving us a sample size of 421 and 281 PW in each arm (or 842 and 562 women in the full trial).

We used Hb data provided by the Suaahara nutrition programme 2017 annual survey (90) from the neighbouring plains district of Rupandehi, to inform our sample size estimates. These data, which were sampled on the basis of old VDC old wards that are the same as our cluster definition, provided a standard deviation (SD) of Hb of 1.2 and an intracluster correlation coefficient (ICC) of 0.09.

A Cochrane review showed a mean difference of Hb 0.888 g/L (95% CI 0.696 to 1.080) between PW supplemented with iron versus women without supplements (43). Since in our control clusters we expect lower intakes of IFA and iron-rich food than in intervention clusters, we consider a 0.4g/dL difference in Hb at 30±2 weeks of gestation between trial arms plausible. We also consider this effect size to be of clinical importance.

Our power calculations are based on a difference of 0.4 g/dL Hb between arms in the primary outcome, an ICC of 0.09 and SD of Hb of 1.2 (or 1.25) g/dL, and a coefficient of variation (CV) in cluster size of 0.27, based on CAPPT census data. We assume two-sided testing at the 5% significance level. In the best-case scenario of 50% of pregnancies being <20 weeks' gestation, the design provides 88% power assuming a SD of 1.2 and 86% power with an SD of 1.25. Full details of the power available in the different scenarios and details of the number of cases to be enrolled in the full trial (before loss to follow-up) are given in Table 3. Expected pregnancies and population per cluster are provided in Supplementary Annex 7.

Table 3. Power calculations based on different standard deviations and proportion of pregnancies detected <20 weeks

% of pregnancies <20 weeks[1]	No of clusters per arm	Average number of Hb outcomes per cluster	ICC (rho)	CV cluster size	Detectable difference in Hb	Power with SD of 1.2	Power with SD of 1.25
50%	27	15.6	0.09	0.27	0.4	88.3%	85.7%
33%	27	10.4	0.09	0.27	0.4	82.1%	79.0%

[1] enrolment cut-off is ≤19 weeks 6 days gestation

Recruitment [15]

Strategies to achieve adequate participant enrolment to reach the target sample size include monitoring menstruation of all consenting non-pregnant eligible women in the cluster and a free urine pregnancy test (UPT) after one or more missed menstrual period so that pregnancies are enrolled before 20 weeks. We provide FCHVs a monthly travel allowance plus an additional incentive on the basis of pregnancies detected. We conservatively accounted for only 33 to 50% of pregnancies being detected <20 weeks, 20% loss to follow-up, and will allow one month for trial run-in to iron out problems at the start. To increase the response rate in later pregnancy, we provide an incentive to trial participants (NPR 1000) at the 30±2-week interview.

Assignment of interventions: allocation

Sequence generation [16a]

To randomly allocate clusters to two arms we used covariate-based constrained randomisation, drawing upon census data to characterise clusters to enable a similar population composition between study arms. The trial statistician (AC) randomly generated 5000 potential allocations based on computer-generated random permutation, from which 4206 were rejected on the basis of any of the following thresholds for the difference in cluster mean between arms:

- Difference in % Muslim more than 5
- Difference in % hills ethnicity more than 2
- Difference in number of eligible women more than 17

- Difference in travel time to health centre on foot more than 3.5 minutes
- Difference in travel time to health centre by vehicle more than 2 minutes

These thresholds were set at approximately 0.25 of the SD in cluster summary value across the 54 clusters for each covariate and were considered adequate for good balance. We did not restrict the randomisation more strictly because of concerns this might impact on the type 1 error, for example as pairs of clusters tended to be allocated to the same arm. The remaining 794 candidate allocations were found unique and 12 were selected at random. A final list of 24 potential allocations was prepared, in which each of the 12 allocations was applied in the 2 possible ways (0/1 is either control/intervention or intervention/control) to ensure exactly equal chance of each cluster being allocated to control or intervention.

Concealment mechanism [16b]

To ensure the randomisation process was observed to be fair, we held a meeting with municipality and health system leaders in March 2021 where we introduced the trial and invited a leader to randomly pick out the chosen randomisation option from a box of ping-pong balls labelled with the randomisation number. The allocation to arms was revealed to stakeholders and trial team members at the same moment in this public forum by a community stakeholder opening a sealed envelope with the chosen randomisation sequence and reading it out to the group.

Implementation [16c]

The potential cluster allocation sequences were generated by the trial statistician (AC), and the final selection at the meeting (as described above) was made in advance of any recruitment of participants. Participants will be enrolled by field staff on the basis of meeting eligibility criteria and their cluster of residence determines allocation.

Assignment of interventions: Blinding

Who is blinded [17a]

After assignment of clusters to study arms, blinding of trial staff and participants is impossible, since the interventions are implemented at a cluster-level and are publicised amongst community representatives, health workers, and policymakers, to increase intervention uptake. Data collectors who collect primary

outcome haemoglobin measurements and other secondary outcomes will know the study arm of the participant at the time of data collection, but since the Hb reading is a digital read out from a Hemocue analyser, the risk of bias in collection of the primary outcome is low. Interim reports for the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) regarding recruitment, follow-up and baseline characteristics are unblinded. Interim safety reports (morbidity and side effects) for the DMC will be initially blinded but can be unblinded on request of the DMC if differences are observed.

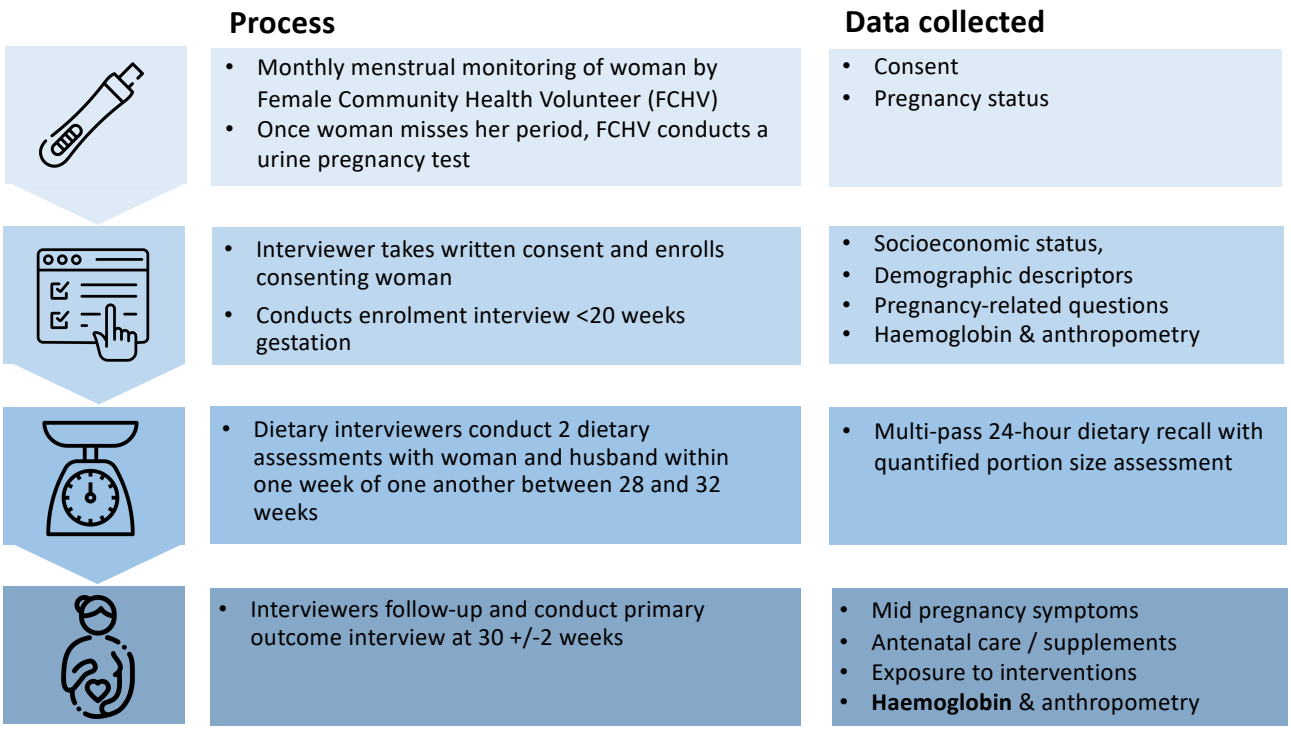
Data collection and management

Plans for assessment and collection of outcomes [18a]

A chart outlining the surveillance system is provided in Figure 6.

103 incentivised FCHVs, with support from 8 interviewers, will monitor menstrual status in paper registers every 4 weeks. Interviewers collect data on all trial participants at enrolment (<20 weeks') and at 30±2 weeks' gestation, covering primary, secondary and process outcomes. Six specialised dietary data interviewers undertake two 24-hour dietary recalls at 30±2 weeks' gestation on non-consecutive days but within approximately one week of one another. They interview the woman and her husband/or a senior adult male household member if the husband lives away. If there are no adult males, the mother-in-law (or other female household head) is interviewed.

Figure 6. Surveillance system process



Electronic data collection

Questionnaires are programmed in Nepali, Awadhi, and English on android operating system tablets or mobile phones using the CommCare electronic data collection platform (91). In-built jump-sequences and value limits prevent entry of data outside plausible ranges.

To enable seamless merging of data by participant and efficient case management and follow-up, unique identifiers (IDs) encoded into Quick Response (QR) codes are printed onto stickers. These are allocated to women enrolled by attaching them next to their names in menstrual monitoring registers. When a woman is enrolled in the trial her QR code is attached to her a trial participant card (TPC) and to a trial participant list held by each interviewer. Her ID is scanned at every interaction with interviewers, dietary interviewers, and NAs, enabling information stored in CommCare about that woman (such as name, LMP, and other details) to be 'called up' and used to ensure questionnaire flow and accuracy.

Standard operating procedures

To standardise haemoglobin concentration (Hb) measurements, anthropometric, and 24-hour dietary recall measurements, standard operating procedures (SOPs) are followed to ensure that measurements are

accurate and inter-observer difference minimised. Hb is determined using a portable battery-operated electronic Haemoglobin Photometer (Hemocue Hb 301+, Angelhom, Sweden). The haemoglobin measurement follows standard procedures as per manufacturer's instructions. Anthropometric measures are taken following WHO guidelines (92, 93). Mid-upper arm circumference (MUAC) and weight of women and their husbands are measured using Seca head circumference tapes (93/42/EEC) to nearest mm, and Seca 877 weighing scales accurate to 100g respectively. Heights are measured using portable Leicester Stadiometers. Calibration of Hemocue and scales are checked at least once per week by the interviewers. Videos on how to take anthropometric and Hemocue measurements have been developed for use during training and are installed on their tablets for reference. Interviewers' tablets will be programmed to provide reminders for calibration checks and COVID-19 symptom checks as required. In the case of anthropometric measures, a third reading is required if the first two measures differ by more than a specified margin. Dietary intake assessments will follow standard protocols (94), including a five-stage multi-pass probing method to minimise underreporting (95).

Enrolment of trial participants

FCHVs are responsible for detecting pregnancies in their cluster as early as possible. Initially, the FCHVs and interviewers visit every identified woman to take her written consent for ongoing menstrual monitoring and to update information from the census (adding new women and households as appropriate). After consent has been taken in all clusters, trial enrolment starts. FCHVs record each consenting women's LMP in the page of the register corresponding to her unique ID. The FCHVs subsequently visit every 4 weeks to record women's menstrual/pregnancy status over a period of 7 months.

Once an FCHV finds a woman who has missed at least one period, she conducts a urine pregnancy test (UPT) at the woman's house. If the UPT is positive, the interviewer visits the woman to check her eligibility and take her written consent to enrol in the trial. The interviewer provides each consenting eligible woman with a TPC with her unique QR code identification number affixed. If a woman is ineligible (≥20 weeks' gestation, not planning to reside in the cluster, or unable to respond to questions) she is advised to seek ANC and, in the intervention arm only, is invited to join PLA women's groups. In intervention clusters,

interviewers notify the NAs about the location and gestational age of the newly enrolled eligible women to receive her first home visit and invite her to PLA groups.

When the interviewer takes informed written consent from women, they ask 5-6 questions to check the PW's understanding of trial process. Only those who can demonstrate that they have understood are enrolled. At both enrolment and primary outcome interactions, interviewers will measure the woman's haemoglobin concentrations, height, weight, and mid-upper arm circumference. We will also collect the woman's age, parity, medical history, date of the last menstrual period, pregnancy symptoms/ problems, pregnancy intention as measured by the London Measure of Unwanted Pregnancy (LMUP), smoking and alcohol consumption, age of husband, household size, and other socioeconomic and demographic information including caste/religion, education, landholdings and assets, and housing characteristics.

Outcome measurement in the third trimester of pregnancy

As listed in Table 1, all primary, secondary and process outcomes are measured at 30±2 weeks. Although ideally during the 28-to-32-week window, due to potential disruption that the ongoing covid-19 pandemic may cause, an outcome may be collected any time up to delivery as gestational age at measurement will be adjusted for in all analyses.

Dietary interviewers use an adapted quantitative 24-hour dietary recall tool (96) to measure dietary intakes of PW and their husbands or another 'senior' male (or a female household head if there are no men). Recalls are taken twice on non-consecutive days after between 28 and 32 weeks, including typical and atypical (celebratory and fasting) days. Daily nutritional intakes are calculated using (i) a list of locally available foods; (ii) quantified intakes of each food, estimated using a combination of weighed methods (using food models) and a photographic atlas of graduated portion sizes (97) and (iii) a Food Composition Table that integrates nutritional composition data from Nepal (98-100), India (101), Bangladesh (102), United States (103), UK (104, 105) and published back-of-pack information from local foods (100).

Monitoring and Supervision of Data Collection

All interviewers are supervised by field co-ordinators and a monitoring manager who observe 5% of interviews, take replicate measures of anthropometry and monitor electronic form submissions. The

monitoring team meets monthly and Kathmandu-based team members visit and/or hold video-conferencing meetings periodically to provide support. Problems with electronic forms are logged and corrections made reversibly in the data using Stata data cleaning 'do' files. A Kathmandu-based data management team monitors data daily.

Plans to promote participant retention and complete follow-up [18b]

Strategies to promote participant retention include collecting and updating phone numbers of respondents so interviewers can arrange a convenient time to visit; and providing a small gift at the end of data collection. Within the CommCare forms, target dates for intervention and follow-up events, based on the LMP, are displayed on customised lists by user to help interviewers follow the schedule.

Data management [19]

Data are stored in the following places:

- FCHVs hold paper registers for menstrual monitoring
- Interviewers have lists of women enrolled in menstrual monitoring permanently stored on password-protected tablets, and survey data are temporarily stored before they are synchronised (encrypted) to a CommCare cloud server. Essential information required for case management is retained on the devices within the CommCare to facilitate follow-up and questionnaire flow.
- Enrolled women have a copy of some of their own data, recorded on their trial participant cards
- Health facilities are provided with enrolled women's names and the IFA and albendazole prescribed by NAs.
- HERD International's data management team in Kathmandu downloads all new data daily from the CommCare cloud server onto their server using a semi-automated system to extract csv files, import them into Stata and run automated do files for data pseudonymising, labelling and recoding.

Pseudo-anonymised data are shared with other data team members as needed but the person-identifiable information is stored in separate encrypted files, which are not used day-to-day unless follow-up lists need to be generated or maintained by authorised team members. Follow-up lists and data collector

performance outputs are uploaded to a shared folder for the field managers and data coordinators to perform their checks.

All data are stored on password-protected, encrypted, secure server computers in lockable rooms at the Kathmandu office. Data on physical servers are backed up daily onto secure cloud servers and copied onto external secure backup hardware-encrypted hard drives in Kathmandu each week. The pseudonymised files are shared with named analysts / data managers for inspecting data quality and generating data summaries for the Data Management Committee and Trial Steering Committee as appropriate. Study arm is encoded but not labelled. Once all of the data have been collected and uploaded to the secure server and follow-up is complete, the data are deleted from supervisors' laptops and data collection tablets, and eventually from the CommCare server.

Qualitative data collected in Awadhi and Nepali languages are transcribed in Nepali. After transcription, qualitative data collectors send audio recording and transcriptions to the HERD Kathmandu office where core team members check completeness, anonymisation and store the data in a lockable cabinet. The transcribed anonymized data is then translated to English, cross-checked with the original Nepali transcripts, and thematically analysed.

Data Cleaning

Data cleaning is completed by HERD International Data Management teams, NS and HHF as required. Variable naming, labelling and initial recoding is automated at the time of downloading. For all outcomes and important process variables and covariates, variable distributions are checked for normality, skewness and outliers identified and removed as necessary.

Data Archiving

After the trial is complete the pseudonymised trial master file, including all datasets, is securely stored electronically with trial partners in HERD, UCL and LSHTM. Both pseudonymised and person-identifiable data are uploaded to the UCL Data Safe Haven along with the questionnaires, data codebook and brief description of the trial. Archiving of data in Nepal follows HERD International's and NHRC policies.

The pseudonymised data will be made open access using the UCL data sharing platform or similar as per MRC guidelines. Any request for archived person-identifiable data will go through the trial management team.

Confidentiality [27]

During the consent process, study participants are assured that all person-identifiable information will not be attached to the data used for analysis. They are also assured that the information they share with FCHVs regarding their menstrual or pregnancy status and any details recorded on data forms will not be shared with anyone in the community. Participants consent to their names and contact details being kept on follow-up lists on phones, tablets, computers, registers, and paper lists but that this information are accessible only to specified members of the data management team and to the field team members that need to visit them during follow-up. They are told that the details of any IFA and deworming provided to them is shared with local health facilities to avoid double dosing. They understand that they will not be identifiable in the data that is used for the study analysis or in any data shared within and beyond the study team.

If a participant withdraws from the study after data are anonymised and shared for analysis, it may not be possible to remove their data, but we can assure them that they can be removed from follow up lists in the future, if they do not wish to be contacted.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use [33]

No storable biological specimens are collected during this study.

Statistical methods

Statistical methods for primary and secondary outcomes [20a]

A detailed Statistical Analysis Plan, drawn up by the trial statistician (AC) and Nepal principal investigator (NS), will detail the analysis strategies, covariate adjustment, and the approach to any missing data. Each

834 version is presented to the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) for
835 approval and the first version is prepared before the first patient is recruited.
836 Primary analysis is by intention-to-treat and will use the standard 5% significance level. Analysis of the
837 primary outcome (haemoglobin concentration at the 30±2 weeks) is based on linear regression, with
838 random effects to adjust for clustering. Analyses are conducted with and without adjustment for predictors
839 of the primary outcome including socioeconomic status, parity, age of PW, gestational age at
840 measurement, maternal education, and characteristics used in the restricted randomisation (individual
841 level religion, ethnicity, and travel time to the nearest health facility and cluster-level number of eligible
842 women from the pre-trial census).
843 Our primary analysis will also adjust for haemoglobin at enrolment, to gain precision, but we acknowledge
844 the trade-off that this may dilute intervention effects since in principle cluster-level intervention effects
845 could be mediated through haemoglobin at enrolment. In a sensitivity analysis we will remove adjustment
846 for haemoglobin at enrolment.
847 Analysis of secondary and impact pathway outcomes (Table 1) and of process indicators (reported in 1 or
848 more separate publications (Table 2)) will follow a similar methodology. We will use linear regression for
849 continuous outcomes, logistic regression for binary outcomes, ordinal logistic regression for ordinal
850 outcomes and negative binomial regression for 'count' outcomes such as number of IFA consumed. For
851 continuous and count outcomes, before analysis of intervention effectiveness, the distribution will be
852 examined and in the event of skewed or heaped data transformations such as log will be considered, or
853 methods will be adapted such as for zero-inflation. For energy, iron, and other micronutrients, which are
854 (almost) ubiquitously consumed, we will use our duplicate measure to account for the wide intra-individual
855 variability with a non-linear random effects model and person-specific random effects (the National Cancer
856 Institute method). For intakes of recommended foods that are only episodically consumed but also have
857 wide within-person variance, we use a two-part model where the probability of consumption is estimated
858 using a multilevel logistic regression, the amount consumed on consumption days is estimated by fitting a
859 multilevel nonlinear regression model, and the error terms of the two parts are correlated (106).
860

Table 4. Variables to adjust for or to use in sub-group analyses and exposure variables

Confounders / covariates to adjust for in analyses:
Wealth score constructed out of household assets
Education status of pregnant woman (none, primary, secondary, higher secondary +)
Parity (n)
Age of pregnant woman in years
Gestational age at measurement in weeks
Baseline (study enrolment) measure of Hb (for primary outcome analysis)
Adjustments for study design
Religion (Muslim versus Hindu)
Ethnicity (hills versus plains)
Travel time to health facility
Cluster size (number of eligible women identified in the cluster during the census as used during constrained randomisation)
Cluster (as random effect)
Variables to use in subgroup analyses
Baseline (study enrolment) anaemia status
Categories of BMI at enrolment (kg/m^2)
Wealth categories constructed out of household assets
Main exposure (independent) variable for analyses of outcomes above:
Study arm: Home visiting +PLA versus Control (which is the reference group)
Within the intervention arm the levels of exposure to PLA women's groups and home visits are coded in three (independent) variables for analyses of a dose-response effect upon the outcomes above (or a subset of them):
Exposure to women's group – score of exposure constructed out of number of meetings attended by pregnant woman and number attended by family members
Exposure to home visiting with tailored counselling and dose of iron folic-acid supplements – score of exposure constructed out of number of meetings attended by pregnant woman and number attended by family members
IFA consumption during pregnancy (count or ordinal score constructed from the count)

Interim analyses [21b]

No interim analyses of intervention effectiveness are planned. Interim reports for the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) regarding recruitment, follow-up and baseline characteristics will be prepared and interim safety reports (morbidity and side effects) for the DMC.

Methods for additional analyses (e.g., subgroup analyses) [20b]

Subgroup analyses will compare the intervention effect on the primary outcome by socio-economic status, BMI category at enrolment and by baseline anaemia status. The intervention effect is presented within subgroups, and testing for differential effect by subgroup is based on an interaction term, using the same regression approach as for our main analyses.

Our main analyses are under the intention-to-treat principle, i.e., as randomised at the cluster level regardless of uptake of home visits, tailored IFA dosage or PLA. However, for the primary outcome we will also conduct a 'per protocol' analysis in which participants who received the intervention only (i.e., who had PLA groups running in their community and received at least one home visit) are compared to all participants in the control arm.

Within the intervention arm we will analyse the dose-response effect upon the primary outcome. Three separate exposure scores will be derived based on the: (1) number of home visits received, and number of family members engaged during visits, (2) number of PLA meetings attended by PW and number attended by family members and (3) number of IFA consumed. We will investigate the association between each score and the primary outcome, with and without adjustment for the other scores.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data [20c]

We expect very low missing data in our baseline covariates and in the haemoglobin measure at enrolment. We do anticipate some women will not have a primary outcome value. Where this is due to miscarriage, we do not regard this as 'missing', but where the woman is unavailable or has moved away, we consider this to be missing. We do not however consider that imputation of the primary outcome is helpful since there is little information on which to base the imputation other than baseline/enrolment measures, which we are including as covariates in our regression models.

Plans to give access to the full protocol, participant level-data and statistical code [31c]

Two versions of the trial protocol are publicly available, a longer version published on the ISRCTN registration page and a published protocol in a peer reviewed journal.

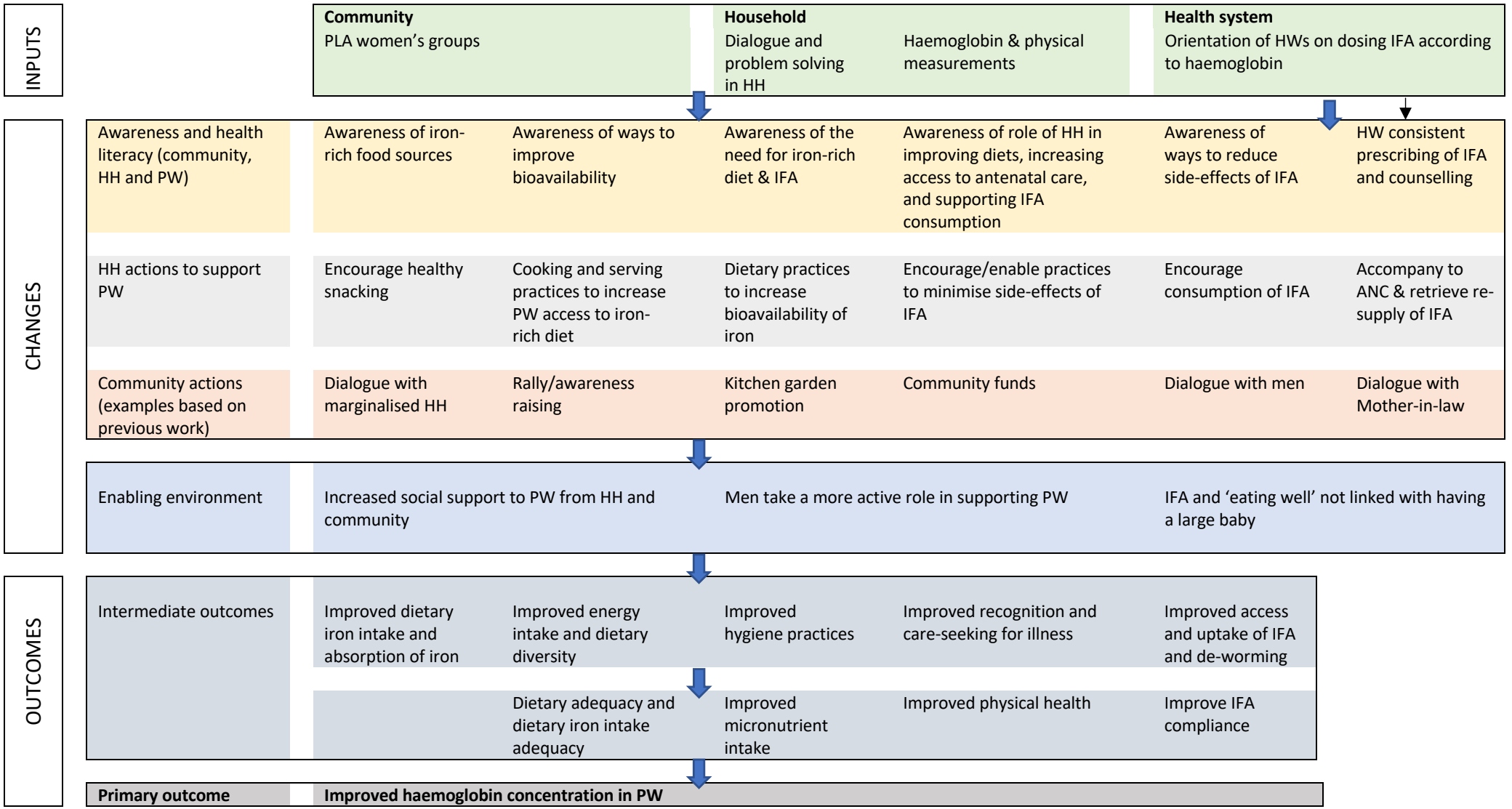
Participant-level data will be shared only at the time of the publication of the main trial paper but will be made fully available subsequently. Statistical code for conducting the trial analysis will be shared in a web annex to the main trial paper.

Process evaluation

Our process evaluation is informed by MRC guidance and our theory of change (Figure 7), and captures how the intervention was implemented, fidelity to plans, reach of the intervention, pathways to impact, and contextual factors that explain heterogeneity in effects. The Theory of Change was developed through two workshops and refined after reviewing formative research findings. It details the hypothesised mechanisms which will enable change in our primary and secondary outcomes in intervention areas and the assumptions that underpin them.

Quantitative process outcomes, captured through surveillance questionnaires, have been included in Table 2. We explore how the context in both intervention and control areas may influence intervention effect (107). We will describe the implementation of the intervention and fidelity to plans through analysis of process monitoring forms administered by supervisors of NAs. A senior process evaluation officer will review these data, and conduct focus group discussions with supervisors and NAs three times during through the intervention to explore how context affected the implementation of the intervention, and to analyse factors affecting attendance at groups and exposure to home visits. If we find effects on our primary outcome, we will use mediation analyses to unpack pathways along our theory of change, exploring whether effects are explained by changes in health literacy, social norms, dietary iron intakes, other micronutrient intakes, IFA compliance, or deworming.

Figure 7. Theory of Change



Economic evaluation

Cost and cost-effectiveness of the intervention will be estimated from a provider perspective. The costs of design and implementing the intervention package (program costs) and costs to public health care providers will be estimated. Program cost data will be collected from the project accounts of the implementing partner, staff time use surveys and interviews with project staff. Costs to public health care providers as a result of any increased demand for health services caused by the intervention, will be estimated using health seeking data from the 30±2 week questionnaire with the study participants and available secondary data on unit costs for the services in question. Incremental cost effectiveness of the intervention package will be calculated as compared to routine care. Incremental cost-effectiveness ratios (ICERs) will be estimated for the primary outcome and for associated disability-adjusted life years (DALYs) averted. A series of sensitivity analyses will be conducted to check the robustness of the results.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee [5d]

Nepal Trial Management Committee: Sara Hillman, Naomi Saville, Sushil Baral, Joanna Morrison, Abriti Arjyal, Andrew Copas, Helen Harris-Fry, Sanju Bhattarai

Trial Steering Committee

The Trial Steering Committee will follow a charter which can be found in Supplementary Annex 8 and will comprise the following members:

Independent Chair: Prof Peter Brocklehurst (independent expert 1 with experience of conducting trials in low-income settings on women's health). Professor of Women's Health, Director, Birmingham Clinical Trials Unit (BCTU), Institute of Applied Health Research, University of Birmingham. Email: p.brocklehurst@bham.ac.uk

Independent expert: Dr Kevin H.M. Kuo, MD, MSc, FRCPC (Haematologist with specialism in red cell disorders), Clinician-Investigator and Staff Hematologist, Division of Hematology, Department of Medicine, Faculty of Medicine, University of Toronto Email: kevin.kuo@uhn.ca

Experts from Nepal:

Dr. Madhu Dixit Devkota – Nepal representative for maternal health and nutrition, Chairperson Neuro Hospital, Kathmandu, Nepal. Previously Professor of Public Health Institute of Medicine, Tribhuvan University. Board member Nepal Health Research Council, Member of National Nutrition and Food Security Steering Committee, Kathmandu, Nepal. Email: madhudevkota@gmail.com

Experts from India: Dr Shalini Singh - India representative from Indian Council of Medical Research, Division of Reproductive and Child Health Maternal health, New Delhi. Email: shalinisingh@icmr.org.in

Prof. Umesh Kapil – India nutrition specialist. Human Nutrition Unit, AIIMS, New Delhi, India. Email: umeshkapil@gmail.com

List of investigators on the Trial Steering Committee

Dr. Sara Hillman - Overall PI, Clinical Training Fellow /NIHR Lecturer, Maternal & Fetal Medicine, UCL Institute for Women's Health. Email: sara.hillman@ucl.ac.uk

Dr. Naomi Saville – Local co- Principal Investigator for Nepal, Senior Research Associate, UCL Institute for Global Health (based in Nepal). Email: n.saville@ucl.ac.uk

Prof Andrew Copas - Trial Statistician, jointly in the UCL Institute for Global Health and the MRC Clinical Trials Unit. Email: a.copas@ucl.ac.uk

Dr. Sushil Baral, HERD – Local co-principal investigator of Nepal trial, Managing Director of HERD, Kathmandu, Nepal. Email: sushil@herdint.com

Ms. Sanju Bhattarai - Nepal Trial coordinator, HERD, Kathmandu. Email: sanju.bhattarai@herdint.com

Dr Helen Harris-Fry – specialist in dietary assessment, London School of Hygiene and Tropical Medicine (LSHTM) Email: helen.harris-fry@lshtm.ac.uk

Observer from MRC:

Ms Melissa.Lennartz-Walker, Newton Fund programme Manager, (MRC), 2nd Floor David Philips Building, Polaris House, North Star Avenue, Swindon, SN2 1FL Email: Melissa.Lennartz-Walker@mrc.ukri.org

Composition of the data monitoring committee, its role and reporting structure [21a]

The Data Management Committee will follow a charter which can be found in Supplementary Annex 9 and will comprise the following members:

973 Chair: Professor Keith West, Program Director, Human Nutrition Johns Hopkins University USA

974 Dr James Martin, Research Fellow (Statistician), Institute of Applied Health Research, University of

975 Birminghan, Birmingham, B15 2TT, UK j.t.martin@bham.ac.uk

976 Dr. Rajendra Kumar BC -Research Advisor, Nepal Health Research Council, Kathmandu, Nepal. Research

977 Team member of Nepal Micronutrient Status Survey (2016). Email: drrajendra2005@gmail.com

978 Dr Meghnath Dhimal, Chief / Senior Research Officer, Health Research Section, Nepal Health Research

979 Council, Kathmandu, Nepal. Email: meghdhimal@gmail.com

980 Dr Shobha Rao, Professor in Biometry and Nutrition Unit, Agharker Research Institute, Pune Pune Maternal

981 Nutrition Study. Email: raoari@yahoo.com

982 Dr Evangelia Koumoutsea, Obstetric Haematologist- Division of Hematology, Department of Medicine,

983 Faculty of Medicine, University of Toronto. Email: evangelia.koumoutsea@uhn.ca

984

985 The charters of the Trial Steering Monitoring and Data Monitoring Committee are provided in

986 Supplementary Annexes 8 and 9.

987

988 We do not specify a formal stopping rule since the interventions under test are simply adapting WHO and

989 government policies for IFA supplementation that are already in use. So, whilst women may consume more

990 IFA tablets as a result of the intervention there is no new drug being tested. The risk during the finger prick

991 test for Hemocue testing to know the haemoglobin status is low. We also do not intend to consider

992 modification or early stopping of the trial on the basis of interim evidence of intervention effectiveness (or

993 lack of effectiveness). Nevertheless, the DMC is presented with harms data (adverse events and levels of

994 morbidity) disaggregated by study arm at each meeting and could recommend to the Trial Steering

995 Committee modification or termination of the trial.

996

997 **Adverse event reporting and harms [22]**

998 Surveillance questionnaires and questions posed during counselling sessions will assess side effects of

999 taking IFA which we expect will mostly be mild symptoms including dark stool, nausea, bloating, abdominal

discomfort, heartburn, loss of appetite, metallic taste, and constipation. The most serious problems that could arise may be a severe allergic reaction to IFA (though this is very rare) or participants contracting COVID-19 after interacting with a trial team member. In addition, our primary outcome questionnaire will record recalled symptoms of illness including pre-eclampsia, vaginal bleeding, dysentery, gestational diabetes, and malaria, though none of these are expected to be associated with our intervention. Although we do not expect any adverse effects of attending a PLA group, of being visited for counselling or interviews/measurements, we will establish a complaints procedure and ensure that trial participants and their families know who to call or where to visit to register a complaint. Contact details are provided in the participation information sheet, and participants will be reminded of the complaints procedure at each visit.

If any unanticipated effects (including maternal deaths or COVID-19 cases associated with trial participation) are noted by the NAs, interviewers, or dietary data collectors, they will inform field co-ordinators / managers who will telephone and/or visit the home of the respondent to ascertain the extent and nature of the problem and complete an adverse events form. Investigators will then classify each event as a Minor Adverse Reaction (MAR), Severe Adverse Reaction (SAR), Severe Adverse Event (SAE), or Suspected Unexpected Serious Adverse Reaction (SUSAR). These will be presented to PIs and to the Data Monitoring Committee where appropriate. In the case of illness, all participants are referred to the appropriate referral centre depending on the severity of their condition.

Harms associated with COVID-19 and their mitigation

The COVID-19 pandemic raises new issues with respect to potential harms to study participants and /or to research team members. Depending on the levels of COVID-19 in the community, visiting women in their homes and calling community groups together may incur risk of increasing the spread of the disease, putting participants, trial implementers, their families, and communities at risk. The measurements that need to be taken in interviews and during home visits require physical contact. PLA groups require communities to gather together, often in quite cramped conditions to keep out of the sun or rain, which makes keeping a distance of 2 metres between group participants impossible.

Because of these risks, the CAPPT trial enrolment and follow up was delayed between March 2020 and February 2021. Preparations were cautiously being initiated for enrolment to start in June 2021, but these were halted due to a new devastating wave of COVID-19 which began to affect Nepal in April 2021.

We have devised adapted SOPs for COVID-19 Infection Prevention and Control (IPC) involving wearing of a masks by both field team members and study participants at all times during interactions, washing hands with soap and water (or sanitiser) on arrival at a local and before departing, sanitising all anthropometric equipment (stadiometers, weighing scales and MUAC tapes) and Hemocue with antiseptic solution between every use and maintaining two metres distance wherever possible, except when taking readings. For use of picture cards and photographic manuals for data collection, participants will be encouraged to use a stick to indicate pictures rather than touching them. If picture cards are passed around at all they will be laminated and wiped clean with alcohol between interactions.

Before going to the field each morning, each staff member fills a covid-19 symptom data collection form. They also phone the respondents that they are planning to meet that day to fill in the symptom form with them as well. If any symptoms of fever, new cough, anosmia (loss of sense of smell) or any new difficulty breathing are observed or have been observed within the last 14 days in the trial staff member or study participant, or any of their households then the person is considered a suspected covid-19 case. We also check if anyone has tested positive in the last 14 days. In the case that any of the above are positive the interaction will be postponed until the 14-day threshold is reached. After each 14-day period of non-contact the covid-19 screening form is repeated until it is safe for the interaction to be undertaken. If infections increase this may affect the timing of enrolment and follow-up visiting and the fidelity of the intervention to plans.

Frequency and plans for auditing trial conduct [23]

The trial management committee regularly reviews progress of the trial against the timeline and target sample size by arm. Additionally, the trial steering committee and data monitoring committee conduct independent progress reviews (to which the funder (MRC) is invited), as per their Terms of Reference.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) [25]

Any deviation from the protocol is documented and reported to the Principal Investigator, Sponsor, and all other research partners immediately. If major changes to study design are needed during the trial, we will send an amended protocol to the Trial Steering Committee for approval and will seek approval from the NHRC, UCL, and LSHTM ethics boards. We will also amend the entry in the trial registration registry and publish an amendment to this published protocol as follows:

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

Dissemination plans [31a]

In addition to publications in peer-reviewed journals, national- and provincial-level dissemination workshops will be held in Nepal with relevant policy makers, government officials, academics, and other relevant stakeholders to inform them about the trial results. A policy brief will be prepared in English and Nepali and distributed widely at the dissemination events and elsewhere. Trial investigators will seek funds to present findings of the trial and of any ancillary studies in national, regional, and international conferences or workshops wherever possible.

Discussion

We hope that the combination of PLA community groups with two home visits to pregnant women with dialogical counselling and tailored dosing of IFA will result in improved haemoglobin levels, better dietary intakes, and better nutritional status amongst pregnant women. Whether our intervention package is effective or not, the evidence generated by this trial will inform policy and practice to reduce anaemia in pregnancy in Nepal and elsewhere in South Asia.

Supplementary material (provided at the bottom of the document)

Supplementary Annex 1: SPIRIT checklist

Supplementary Annex 2: List of selected study clusters with population and expected pregnancies

Supplementary Annex 3: Menstrual monitoring participant information sheet in English

Supplementary Annex 4: Full trial participant information sheet in English

Supplementary Annex 5: Menstrual monitoring consent form in English

Supplementary Annex 6: Full Trial consent form in English

Supplementary Annex 7. Expected pregnancies to be enrolled and numbers after loss to follow-up

Supplementary Annex 8: Trial Steering Monitoring (TSC) charter

Supplementary Annex 9: Data Monitoring Committee (DMC) charter

Trial status

Protocol version number	Version 1.2	Date: 24 May 2021
Recruitment commenced		Date
Recruitment completion		Date

Abbreviations

Antenatal care (ANC)

Comprehensive Anaemia Programme and Personalised Therapies (CAPPT)

Demographic and Health Survey (DHS)

Female Community Health Volunteer (FCHV)

Government of Nepal (GoN)

Haemoglobin (Hb)

Health Research and Social Development Forum, Nepal (HERD)

International Standard Randomised Controlled Trial Number (ISRCTN)

Iron Deficiency Anaemia (IDA)

Iron Folic Acid supplement (IFA)

Last Menstrual Period (LMP)

London Measure of Unwanted Pregnancy (LMUP)

London School of Hygiene and Tropical Medicine (LSHTM)

Low Birth weight South Asia Trial (LBWSAT)

Low- and Middle-Income Countries (LMICs)

Mean Probability of Adequacy (MPA)

Medical Research Council (MRC)

Mid-Upper Arm Circumference (MUAC)

Ministry of Health & Population (MoHP)

Multiple Indicator Cluster Survey (MICS)

Nepal Heath Research Council (NHRC)

Nepal National Micronutrient Status Survey (NNMSS)

Novel SARS-CoV-2 Corona Virus (COVID-19)

Nutrition Assistant (NA)

Nutrition Education and Counselling (NEC)

Participatory Learning and Action (PLA)

Pregnant woman / women (PW)

Quick Response code (QR code)

Randomised controlled trial (RCT)

Standard Operating Procedure (SOP)

Trial Participant Card (TPC)

Trial Steering Committee (TSC)

University College London (UCL)

Urine Pregnancy Test (UPT)

Village Development Committee (VDC)

Declarations

Acknowledgements

We thank Pankaj Joshi, Subash Gajurel, Romi Giri, Suprich Sapkota, Shophika Regmi, Sanju Bhattarai, Audrey Prost, Vatsla Dadhwal, Aparna Sharma for their contributions in development of this protocol.

Authors' contributions [31b]

NS and CK drafted the first version of the manuscript. All authors provided inputs and read and approved the final paper.

Funding [4]

The study is funded by UK Medical Research Council (MRC)/ Newton Fund (MR/R020485/1).

Note that with matched funding from Indian Department of Biotechnology (DBT) a 'sister' study with the same CAPPT abbreviation is happening in India implemented by AIIMS (All India Institute of Medical Sciences).

Availability of data and materials [29]

The anonymised trial dataset will be uploaded to the UCL data sharing platform at the time of acceptance of the trial paper. The home visiting and PLA manuals will be published for use by other organisations in future.

Ethics approval and consent to participate [24]

Ethical approval has been obtained from UCL ethics committee (Project ID number: 14301/001), Nepal Heath Research Council (NHRC approval number: 353/2019) and London School of Hygiene and Tropical Medicine ethics committee (approval number: 16528).

All correspondence with the NHRC is retained in the trial master file. Substantial amendments that require review by NHRC will not be implemented until permission is granted. The Principal Investigator will notify NHRC of the end of the study, and if the study is ended prematurely, including the reasons for the premature termination. Within one year after the end of the study, we will submit to NHRC a final report with the results, including any publications and abstracts.

Consent or assent

Consent is taken on at cluster, household, and individual levels.

Cluster-level consent

Before initiation of the census, general consent was sought for conducting the trial in that cluster from municipality leaders, municipality-level health system managers, and cluster-level guardians, who is the ward representative for that population cluster. We obtained written permissions from all municipality and ward (cluster) offices for conducting the census and formative activities related to the trial. None of the clusters denied consent.

Individual level consent / assent

During the census, household heads provided written consent for collection of a household roster, household characteristics and information on women of reproductive age. When a female was found eligible for menstrual monitoring during the census, oral consent was taken for her name to be recorded in the menstrual monitoring register and for the interviewer and FCHV to visit her again at the start of menstrual monitoring to take written consent and initiate the 4-weekly visits. For married girls who are under 18 years of age, informed assent is taken as well as informed consent from their guardian at the onset of menstrual monitoring and when a pregnancy is detected. To obtain consent, women are given an explanation of the trial. After hearing information about the study, participants receive a written information sheet about the study. The interviewer asks 5-6 questions to check their understanding of the information in the patient information sheet and once sufficient understanding has been confirmed, they invite her to give informed written consent / assent, in line with international ethical standards for research involving human subjects. If the woman is illiterate, a thumbprint is taken whereas literate respondents will sign the consent form. Both the participant and HERD international keep a copy the signed consent / assent form. If there is any doubt about whether a participant is happy to participate, the participant will not be enrolled. Every participant is given the opportunity to ask questions, and all participants are free to withdraw their consent at any time without providing any reason. They are free to refuse to answer any question or to stop an interview at any time, should they choose to do so. On the rare occasion that the interviewer does not speak the local language, a local translator is enlisted to provide any translation as

necessary, but interviewers speak Awadhi so language should not be a problem. After taking written consent, oral consent is taken at each subsequent interview and home visiting interaction. Informed consent/assent forms and information sheets for menstrual monitoring and full trial participation in English, Nepali, and Awadhi are provided in Supplementary Material S2, S3 and S4 and S5.

Confidentiality

It is necessary to obtain and maintain lists of participants' names to enable women to be followed-up to detect pregnancy and track their progress through pregnancy. It is also necessary to communicate to local and health facilities women's receipt of IFA and deworming at home visits, to prevent double dosing. However, person-identifiable information (names of household members and GPS location) will only be retained by the field staff who need to seek to interact with trial participants and this information will not be made available to others. Apart from follow-up lists, which interviewers and home visitors will utilise, all other data stored on portable, or team members' computers are anonymised such that the participants are identified by their unique ID number but not their name, address, or geolocation.

Person-identifiable information associated with trial participants such as their name and geolocation and signed consent forms are stored in separate encrypted data files in a UCL data safe haven and on encrypted and password protected external media which are stored in locked cupboards kept by the trial PIs and data manager in HERD.

Consent for publication [32]

We have not included any details, images or videos relating to an individual person in this protocol. The written informed consent process for participation in the trial follow up includes the statement "I understand that when I consent to have my photos taken while engaging in the research activities during the research period, that these could be published on HERD international's or UCL's website or other publications." If respondent does not reply "yes" to this during the consent process, no photographs will be taken of that respondent at any point during the study so that there will be no photos of non-consenting individuals.

Competing interests [28]

The authors declare that they have no competing interests

Authors' information

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B. James Beard (BJB), is a freelance consultant specialising in Data management and electronic data collection, Guilford UK. james@beard.net ;

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1513 **Supplementary Annex 1. SPIRIT checklist**

1514

		Reporting Item	Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, lines 2 to 4	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, line 57 and Page 3 ,line 48	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Page 4, line 57	
Protocol version	#3	Date and version identifier	Page 4, line 57	
Funding	#4	Sources and types of financial, material, and other support	Page 4, line 57 and Page 53 line 1137 to 1141	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1, lines 6 to 8 and Page 4 line 57 Contributions given on page 53, lines 1133 to 1135	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	Page 4, line 57	
Roles and responsibilities: sponsor and funder	#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	Page 4, line 57	
Roles and responsibilities: committees	#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)	Page 45-46 lines 933 to 969 and Supplementary Annexes 8 and 9	
Introduction			Page 6 line 83 onwards	
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	Page 6 to 11 lines 84 to 223	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Page 8-9 Lines 210 to 231	
Objectives	#7	Specific objectives or hypotheses	Page 11 to 12, lines 225 to 248	
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, non-inferiority, exploratory)	Page 12 lines 250 to 255	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	Page 12-13, lines 260 to 268	

		where data will be collected. Reference to where list of study sites can be obtained		
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)	Page 13 to 16, lines 269 to 336	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 15 to 23 lines 374 to 489 Figures 3 to 4	
Interventions: modifications	#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)	Page 22, lines 490 to 501	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 24-25, lines 503 to 522	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 25, Lines 524 to 529	
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	Page 25 -27, Lines 536 to 564	
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)	Page 27 to 29, Lines 566 to 580. Figure 5	
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	Page 30 to 31, lines 581 to 611	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 31, lines 613 to 621	
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	Page 31-32, lines 622 to 640	
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	Page 32, lines 642 to 648	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 32 lines 649 to 653	

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Page 32 to 33 lines 654 to 664	
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Page 33, lines 661 to 664	
Methods: Data collection, management, and analysis				
Data collection plan	#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	Page 33 to 37, lines 666 to 761. Figure 6	
Data collection plan: retention	#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	Page 37 lines 762 to 766	
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	Page 37 to 39, lines 767 to 826	
Statistics: outcomes	#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	Page 39 to 41, lines 831 to 867	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 41 - 42 lines 868 to 882	
Statistics: analysis population and missing data	#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)	Page 42, lines 884 to 891	
Methods: Monitoring				
Data monitoring: formal committee	#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	Page 46 to 47, lines 971 to 996 and Annex 9	
Data monitoring: interim analysis	#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	Page 46, lines 989 to 996	
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	Page 47 to 49, lines 998 to 1047	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 49, lines 1049 to 1052	

Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Page 53, lines 1148 to 1155	
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)	Page 50, lines 1053 to 1060	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 53 to 55, lines 1157 to 1187	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 54, Annexes S3 to S6	
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	Page 55, lines 1189 to 1201	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 56, lines 1211 to 1212	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 39 lines 809 to 811. Page 42, lines 893 to 898	
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	Page 25, lines 531 to 533	
Dissemination policy: trial results	#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	Page 50, lines 1069 to 1074	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	Page 53 lines 1133 to 1135	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Page 42, lines 893 to 898	
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary Annexes 3 to 6	
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	Page 39, lines 827 to 829.	

Supplementary Annex 2: List of selected study clusters with population and expected pregnancies

1. Cluster number	2. Name of old VDC	3. Cluster Code	4. old-ward 1	5. old-ward 2	6. cluster is 1 old-ward	7. Women who consented to eligibility check (n)	8. Households that consented to the census	9. Female pop' (n)	9. Male pop' (n)	10. Total pop' (n)	11. MWRA (13-49 years) (n)	12. Eligible MWRA consenting to menstrual monitoring follow-up (n)	14. Exp. preg/m 2.52 pr 1000 population (n)	15. Exp. preg/m if 50% are <20 weeks (n)	16. Exp. preg/ m if 33% are <20 weeks	17. Exp. preg/m after 20% LTFU if 50% are <20 weeks (n)	18. Exp. preg/m after 20% LTFU if 33% are <20 weeks (n)	19. Exp. preg. over 6 m	20. Exp. preg. over 6m if 50% are <20 weeks (n)	21. Exp. preg. over 6m if 33% are <20 weeks (n)	22. Exp. preg. over 6m after 20% LTFU if 50% are <20 weeks (n)	23. Exp. preg. over 6 m after 20% LTFU if 33% are <20 weeks (n)
1	Hathihawa	Ha1	2	4	0	427	482	2,090	2,165	4,255	750	408	10.7	5.4	3.2	4.3	2.6	64	32.2	21.4	25.7	17.2
3	Bijuwa	Bij1	5	8	0	382	410	1,671	1,838	3,509	696	331	8.8	4.4	2.7	3.5	2.1	53	26.5	17.7	21.2	14.1
4	Baskhore	Ba1	7	9	0	376	402	1,762	1,828	3,590	703	366	9.0	4.5	2.7	3.6	2.2	54	27.1	18.1	21.7	14.5
7	Lawani	L1	3	7	0	243	267	974	1,082	2,056	407	228	5.2	2.6	1.6	2.1	1.2	31	15.5	10.4	12.4	8.3
8	Patariya	Pat1	4	7	0	555	613	2,373	2,492	4,865	928	480	12.3	6.1	3.7	4.9	2.9	74	36.8	24.5	29.4	19.6
9	Bithuwa	Bit1	5	6	0	253	276	1,416	1,452	2,868	565	225	7.2	3.6	2.2	2.9	1.7	43	21.7	14.5	17.3	11.6
11	Abhirao	A1	8	9	0	285	324	1,294	1,342	2,636	471	270	6.6	3.3	2.0	2.7	1.6	40	19.9	13.3	15.9	10.6
12	Dumara	Du1	5	7	0	248	265	1,154	1,288	2,442	441	213	6.2	3.1	1.8	2.5	1.5	37	18.5	12.3	14.8	9.8
14	Dharmpaniya	Dha1	1	6	0	274	290	1,227	1,301	2,528	516	245	6.4	3.2	1.9	2.5	1.5	38	19.1	12.7	15.3	10.2
17	Pakadi	Pak1	2	4	0	291	316	1,292	1,285	2,577	527	256	6.5	3.2	1.9	2.6	1.6	39	19.5	13.0	15.6	10.4
18	Pakadi	Pak2	8	9	0	317	340	1,592	1,659	3,251	577	295	8.2	4.1	2.5	3.3	2.0	49	24.6	16.4	19.7	13.1
19	Pipara	Pip1	1	2	0	185	192	1,258	1,416	2,674	442	173	6.7	3.4	2.0	2.7	1.6	40	20.2	13.5	16.2	10.8
21	Rangapur	R1	3	5	0	234	248	1,114	1,159	2,273	461	192	5.7	2.9	1.7	2.3	1.4	34	17.2	11.5	13.7	9.2
23	Parsohiya	Par1	7	8	0	241	256	1,395	1,560	2,955	600	210	7.4	3.7	2.2	3.0	1.8	45	22.3	14.9	17.9	11.9
24	Gauri	Gau1	1	3	0	226	232	1,275	1,348	2,623	500	208	6.6	3.3	2.0	2.6	1.6	40	19.8	13.2	15.9	10.6
25	Gauri	Gau2	8	9	0	215	231	1,042	1,198	2,240	452	200	5.6	2.8	1.7	2.3	1.4	34	16.9	11.3	13.5	9.0
26	Harnampur	Harn1	3	7	0	168	173	927	1,066	1,993	385	145	5.0	2.5	1.5	2.0	1.2	30	15.1	10.0	12.1	8.0
27	Baluhawa	Balu1	2	3	0	352	363	1,731	1,851	3,582	726	317	9.0	4.5	2.7	3.6	2.2	54	27.1	18.1	21.7	14.4
28	Baidauli	Bai1	5	7	0	225	238	1,212	1,157	2,369	448	181	6.0	3.0	1.8	2.4	1.4	36	17.9	11.9	14.3	9.6
29	Somdiha	Som1	1	9	0	169	178	886	1,016	1,902	349	145	4.8	2.4	1.4	1.9	1.2	29	14.4	9.6	11.5	7.7
30	Somdiha	Som2	5	6	0	210	220	992	989	1,981	374	198	5.0	2.5	1.5	2.0	1.2	30	15.0	10.0	12.0	8.0
32	Kajarhawa	Kaj1	1	2	0	188	205	1,080	1,102	2,182	381	176	5.5	2.7	1.6	2.2	1.3	33	16.5	11.0	13.2	8.8
33	Sauraha	Sau1	4	9	0	220	227	827	920	1,747	371	201	4.4	2.2	1.3	1.8	1.1	26	13.2	8.8	10.6	7.0
34	Sihokhore	Si1	4	5	0	209	221	1,020	1,053	2,073	375	200	5.2	2.6	1.6	2.1	1.3	31	15.7	10.4	12.5	8.4
35	Gotihawa	Go1	7	8	0	257	268	1,099	1,187	2,286	444	238	5.8	2.9	1.7	2.3	1.4	35	17.3	11.5	13.8	9.2
36	Sisawa	S1	2	3	0	298	321	1,691	1,902	3,593	619	285	9.1	4.5	2.7	3.6	2.2	54	27.2	18.1	21.7	14.5
37	Kushhawa	Ku1	4	6	0	199	215	1,202	1,358	2,560	448	176	6.5	3.2	1.9	2.6	1.5	39	19.4	12.9	15.5	10.3
38	Kushhawa	Ku2	8	9	0	238	262	1,321	1,456	2,777	485	218	7.0	3.5	2.1	2.8	1.7	42	21.0	14.0	16.8	11.2
39	Ajigara	Aj2	3	4	0	220	240	991	1,089	2,080	378	203	5.2	2.6	1.6	2.1	1.3	31	15.7	10.5	12.6	8.4
40	Ajigara	Aj1	7	8	0	196	214	1,055	1,087	2,142	361	178	5.4	2.7	1.6	2.2	1.3	32	16.2	10.8	13.0	8.6
41	Bhalwari	Bha1	1	7	0	259	279	1,244	1,369	2,613	497	227	6.6	3.3	2.0	2.6	1.6	40	19.8	13.2	15.8	10.5
44	Maharajganj	M3	5	5	1	271	291	1,441	1,598	3,039	483	250	7.7	3.8	2.3	3.1	1.8	46	23.0	15.3	18.4	12.3
45	Bhilmi	Bhi1	3	9	0	251	276	1,328	1,441	2,769	541	231	7.0	3.5	2.1	2.8	1.7	42	20.9	14.0	16.7	11.2
46	Shivanagar	Shiv1	5	7	0	191	221	754	833	1,587	263	177	4.0	2.0	1.2	1.6	1.0	24	12.0	8.0	9.6	6.4
47	Shivanagar	Shiv2	8	9	0	291	337	1,083	1,224	2,307	431	257	5.8	2.9	1.7	2.3	1.4	35	17.4	11.6	14.0	9.3
49	Krishnanagar	K1	7	8	0	318	355	1,400	1,470	2,870	490	281	7.2	3.6	2.2	2.9	1.7	43	21.7	14.5	17.4	11.6
51	Bahadurganj	B2	3	3	1	243	266	1,054	1,119	2,173	404	208	5.5	2.7	1.6	2.2	1.3	33	16.4	11.0	13.1	8.8
52	Bahadurganj	B1	7	7	1	377	396	1,974	2,126	4,100	776	297	10.3	5.2	3.1	4.1	2.5	62	31.0	20.7	24.8	16.5
53	Sirsihawa	Sir1	8	9	0	165	195	817	921	1,738	293	158	4.4	2.2	1.3	1.8	1.1	26	13.1	8.8	10.5	7.0
54	Bhagwanpur	Bh1	1	2	0	176	196	993	1,055	2,048	328	170	5.2	2.6	1.5	2.1	1.2	31	15.5	10.3	12.4	8.3
55	Bhagwanpur	Bh2	7	8	0	244	266	1,623	1,780	3,403	547	226	8.6	4.3	2.6	3.4	2.1	51	25.7	17.2	20.6	13.7
56	Ganeshpur	G1	1	4	0	204	242	858	881	1,739	282	196	4.4	2.2	1.3	1.8	1.1	26	13.1	8.8	10.5	7.0
57	Ganeshpur	G2	2	3	0	184	208	873	936	1,809	299	170	4.6	2.3	1.4	1.8	1.1	27	13.7	9.1	10.9	7.3
58	Pathardaiya	P2	5	5	1	286	332	1,558	1,538	3,096	535	282	7.8	3.9	2.3	3.1	1.9	47	23.4	15.6	18.7	12.5
59	Khurhuriya	Kh2	6	8	0	332	405	1,513	1,535	3,048	524	316	7.7	3.8	2.3	3.1	1.8	46	23.0	15.4	18.4	12.3
62	Bishunpur	Bi1	1	2	0	312	338	1,329	1,392	2,721	486	308	6.9	3.4	2.1	2.7	1.6	41	20.6	13.7	16.5	11.0
66	Manpur	Man1	7	8	0	235	267	1,078	1,157	2,235	456	226	5.6	2.8	1.7	2.3	1.4	34	16.9	11.3	13.5	9.0
67	Mahuwa	Ma1	1	3	0	297	341	1,293	1,409	2,702	500	265	6.8	3.4	2.0	2.7	1.6	41	20.4	13.6	16.3	10.9
68	Mahuwa	Ma2	5	6	0	256	290	1,157	1,186	2,343	396	246	5.9	3.0	1.8	2.4	1.4	35	17.7	11.8	14.2	9.4
69	Balaramwapur	Bal1	2	3	0	228	249	1,063	1,149	2,212	414	223	5.6	2.8	1.7	2.2	1.3	33	16.7	11.1	13.4	8.9
70	Dhankauli	D1	6	7	0	314	330	1,398	1,520	2,918	611	250	7.4	3.7	2.2	2.9	1.8	44	22.1	14.7	17.6	11.8
72	Niglihawa	N1	7	7	1	220	236	896	980	1,876	392	178	4.7	2.4	1.4	1.9	1.1	28	14.2	9.5	11.3	7.6
76	Jahadi	J1	2	9	0	131	172	660	639	1,299	271	114	3.3	1.6	1.0	1.3	0.8	20	9.8	6.5	7.9	5.2
78	Tilaurakot	Ti2	5	6	0	271	334	1,073	1,121	2,194	401	231	5.5	2.8	1.7	2.2	1.3	33	16.6	11.1	13.3	8.8
	Total	**54**	**231**	**334**	**5**	**13,957**	**15,311**	**67,423**	**72,025**	**139,448**	**25,800**	**12,648**	**351.4**	**175.7**	**105.4**	**140.6**	**84.3**	**2108**	**1054.2**	**702.8**	**843.4**	**562.3**
	Mean		*4.3*	*6.2*		*258.5*	*283.5*	*1248.6*	*1333.8*	*2582.4*	*477.8*	*234.2*	*6.5*	*3.3*	*2.0*	*2.6*	*1.6*	*39.0*	*19.5*	*13.0*	*15.6*	*10.4*
	Max		8.0	9.0		555.0	613.0	2373.0	2492.0	4865.0	928.0	480.0	12.3	6.1	3.7	4.9	2.9	73.6	36.8	24.5	29.4	19.6
	Min		1.0	2.0		131.0	172.0	660.0	639.0	1299.0	263.0	114.0	3.3	1.6	1.0	1.3	0.8	19.6	9.8	6.5	7.9	5.2
	Median		*4.5*	*7.0*		*243.5*	*266.5*	*1207.0*	*1286.5*	*2485.0*	*454.0*	*225.5*	*6.3*	*3.1*	*1.9*	*2.5*	*1.5*	*37.6*	*18.8*	*12.5*	*15.0*	*10.0*

44 health facilities

Pop: population; MWRA: Married women of reproductive age; Exp. preg: Expected Pregnancies; LTFU: Loss to Follow-Up.

Supplementary Annex 3: Menstrual monitoring participant information sheet in English

Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Information sheet for menstrual monitoring

Introduction

Namaste! My name is _____. I have come from HERD International located in Thapathali, Kathmandu. HERD International is a national level research organization. This organization has been conducting various programmes and research in the health, environment, and social development. Currently, HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women in Kapilbastu. I would like to invite you to be a part of this study. Before you decide whether to participate, it is important for you to understand why this research is being done and what participation will involve. I will read what is written in this information sheet aloud to you. You can ask me if there is anything that you do not understand or if you want more information. You will be given a copy of this information sheet. Take your time to decide whether or not you want to take part in the study or not. Thank you for reading this/listening to me.

Details of the study

HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women. The Medical Research Council (UK) is funding this research.
Anaemia is a condition when there is decreased haemoglobin in blood, and this is caused by various factors. In Nepal, lack of iron is the most common cause of anaemia in pregnancy. It is important to reduce anaemia in pregnancy because low iron levels are associated with illness and complications during pregnancy and childbirth. Pregnant women who are anaemic are much more likely to die during childbirth
than those women who are not and their infants are more likely to be born small for gestational age.
In Nepal, Kapilbastu is one of the districts where anaemia is highly prevalent. Hence, we have chosen 54 areas (103 old wards) within 9 pallikas of Kapilbastu for this study. We are involving approximately 12700 pregnant women in Kapilbastu district in checking of their pregnancies and aim to enrol 1054 women. This research is designed to find out how anaemia in pregnant women can be reduced in this community and by doing the following:

a. Visiting the home of pregnant women by HERD staff to test their Haemoglobin levels and provide tailored iron-folic acid (IFA) tablets as per their anaemia status and nutrition counselling.
b. Mobilizing women's groups to discuss anaemia, supplements, diet, and antenatal care in pregnancy using Participatory Learning and Action (PLA) method.

Who are we inviting to participate?

We need to enrol 1054 pregnant women who are early in their pregnancy in this study. For this, we need to monitor all the married women in your community to find out when they get pregnant. You can take part in this monitoring if you are a married woman or girl aged 13 to 49 years, living permanently in the study area, and could become pregnant (i.e., you and your husband have not had permanent contraception like laparoscopy, mini-laparoscopy or vasectomy or you have not attained menopause or not had a hysterectomy).

What will happen if you agree to take part in checking of whether you are pregnant or not?

If you agree, your area's *Female Community Health Volunteer* will visit you at home and record information in a register book where we keep your name, address, and ID time. She will visit you every month for the next 7 months to check whether you might be pregnant by asking about your periods. If you have missed a period, she will ask you to give a urine sample to do a urine pregnancy test at your home which will help to confirm your pregnancy status. You do not have to pay money for doing the urine pregnancy test. The *Female Community Health Volunteer* will keep what you say confidential and won't tell your family members or neighbours anything you share with her.

If you turn out to be pregnant and consent to participate in the study, the *Female Community Health Volunteer* will inform a HERD data collector who will visit you and give you a unique ID card and enrol you in the final study. Thereafter, HERD staff members will visit you a further four to six times to enquire about the progress of your pregnancy, diet, and ANC visits. We will measure your height and weight and do a finger prick to get a blood sample to know your haemoglobin level and anaemia status. We will tell you more about this in more detail if you become pregnant.

Are there any risks if you participate?

We do not think that any harm will come to you, but it is possible that you might find sharing information about your periods or pregnancy uncomfortable or upsetting. You don't have to continue to take part if you don't feel like it. If you would like to talk to someone about the feelings generated by the questions, please contact a member of HERD staff.

Are there any benefits if you participate?

If you agree to share your menstrual status each month with your *Female Community Health Volunteer*, we will offer to do a urine pregnancy test in your home after a missed period to confirm your pregnancy. You will not have to buy the urine pregnancy test kit nor pay anyone for doing your urine pregnancy test and you do not have to show the result to anyone except the FCHV. Knowing that you are pregnant at an early stage will help you plan your pregnancy, seek timely and appropriate health care for your unborn baby and eat nutritious food required for proper growth of your baby.

Will my taking part in this project be kept confidential?

All information you share with *Female Community Health Volunteer* or HERD staff will be kept strictly confidential, which means that they are not allowed to tell anyone what you have told them. The information will be recorded either on paper or entered onto mobile phones/ tablets.

In our records, a unique number will be used to identify you. Using this number instead of your name in our data will help to keep your identity anonymous to everyone except those researchers who are directly involving in coming to your house to talk to you. You will not be able to be identified in any ensuing reports or publications.

The kind of information we will keep about you will include your name, age or date of birth, address, and the answers to questions that we ask you or measurements we make on you. This information will be held securely either on paper and/or electronically at HERD International and in University College London in the UK under the provisions the local Data Protection laws. Your name will not be passed to anyone else outside the research team who is not involved in the trial or any future study to follow-up trial participants.

Your records will be available to people authorized to work on the trial and those responsible for ensuring that the study is carried out correctly. By signing the consent form, you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

If you withdraw consent from further study, unless you object, your data will remain on file and will be included in the final study analysis.

In line with Nepal and UK regulations, at the end of the study your data will be securely archived in UK and in Nepal.

Ethical approval

This study has been approved by the Nepal Health Research Council Approval ID number 353/2019, UCL Research Ethics Committee: Project ID number: 14301/001 and London School of Hygiene and Tropical Medicine ethics committee ID number: 16528.

Agreeing to take part

Your participation is voluntary. If you don't want to take part, you can refuse without giving a reason. If you decide to take part in the menstrual monitoring, you will be given this information sheet to keep and be asked to sign or thumb print the consent form. If you agree to participate and then change your mind at any time, please tell us and we will stop visiting you. We will take a photo of the consent form with your signature which will be filed in your records. You can have more time to think this over if you are at all unsure.

More information

You should feel free to discuss the study with other people or ask us any questions.
If you have any more questions, you can contact, Trial Manager, HERD International, Prasuti Griha Marg, Thapathali, Kathmandu. Tel 01-4238045
or
Dr Naomi Saville, Senior Research Associate, University College London Institute for Global Health and Technical advisor to HERD, Kathmandu Nepal. Tel: 01-4238045

HERD International District Office, Taulihawa, Kapilbastu. Tel: number: 076-590090

Thank you for reading this information sheet and for considering whether to take part in this research study.

Supplementary Annex 4: Full trial participant information sheet in English

Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Participant Information Sheet for Pregnant Women Intervention Arm

Introduction

Namaste! My name is _____. I have come from HERD International located in Thapathali, Kathmandu. HERD International is a national level research organization. This organization has been conducting various programmes and research in the health, environment, and social development. Currently, HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women in Kapilbastu. I would like to invite you to be a part of this study.

Before you decide whether to participate, it is important for you to understand why this research is being done and what participation will involve. I will read what is written in this information sheet aloud to you. You can ask me if there is anything that you do not understand or if you want more information. You will be given a copy of this information sheet. Take your time to decide whether or not you want to take part in the study or not. Thank you for reading this/listening to me.

Details of the study

HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women. The Medical Research Council (UK) is funding this research.
Anaemia is a condition when there is decreased haemoglobin in blood, and this is caused by various factors. In Nepal, lack of iron is the most common cause of anaemia in pregnancy. It is important to reduce anaemia in pregnancy because low iron levels are associated with illness and complications during pregnancy and childbirth. Pregnant women who are anaemic are much more likely to die during childbirth than those women who are not and their infants are more likely to be born small for gestational age.
In Nepal, Kapilbastu is one of the districts where anaemia is highly prevalent. Hence, we have chosen 54 clusters (103 old-wards) within 9 pallikas of Kapilbastu for this study. We are involving approximately 1054 pregnant women residing within these 54 clusters. These 54 clusters will be divided equally into 2 groups, each group comprising of 27 clusters and more than 500 pregnant women.
This research is designed to find out how anaemia in pregnant women can be reduced in this community by doing the following:

a. Visiting the home of pregnant women by HERD staff to test their Haemoglobin levels and provide tailored iron-folic acid (IFA) tablets as per their anaemia status and nutrition counselling.

b. Mobilizing women's groups to discuss anaemia, supplements, diet, and antenatal care in pregnancy using Participatory Learning and Action (PLA) method.

Who are we inviting to participate?

You can take part in this research if you are a married woman or girl aged 13 to 49 years, pregnant at less than 20 weeks of gestation, planning to live in this study area for most of your pregnancy and are able to respond to the survey questions.

What will happen if you agree to take part in this study?

If you decide to take part and give your consent (by signing or thumb-printing a consent form), first I will give you a trial participant card with a unique identification number which will be your ID for this study period. I request you to keep this id card in a safe place so that when my other colleagues come to visit you, you can show them this card. You can also show this at the health facility to show the health worker that you are involved in the study. On a tablet, I will record some personal details about you such as your age, education, household details, medical and obstetric history. Also, today I will do a finger prick to obtain blood to test your Haemoglobin level using a Hemocue machine to check whether you have anaemia or not. I will also measure and record your weight, height, the circumference of your upper arm and ask you some questions

about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy.

I will visit you again at around 30 weeks' gestation and measure and record your Haemoglobin, weight, height, and the circumference of your upper arm. I will also enquire about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy.

Another HERD staff (dietary data assistant) may also visit you and your family at around 30 weeks' gestation and again within the same week to ask you and your husband (or another male family member) in detail about what you ate the day before.

A female HERD staff who is an ANM (a "nutrition assistant") will visit you in your home twice during your pregnancy, once at around 12-21 weeks' gestation and another at 18-25 weeks' gestation. At each visit she will discuss with you and your family members about your diet and health in pregnancy and give you advice based on what you are already eating / doing. She will check your anaemia (haemoglobin) level with a Hemocue machine (like we will do today) and tell you about your anaemia status and give you iron folic acid (IFA) tablets as per the standard treatment protocol followed in all government health facilities for treating anaemia in pregnancy.

The nutrition assistant will also invite you and your family members to attend monthly participatory women's groups (PLA meetings), which will be held in your community. You can attend these with a family member or a friend if you would like. The groups are open to anyone in the community. The nutrition assistant from HERD and your FCHV will facilitate these meetings and will discuss the problem of anaemia in pregnancy and how to reduce it through improved diet, eating iron-folic acid (IFA) tablets and going for antenatal care.

I will visit you again at 30 weeks of gestation and measure your haemoglobin level with a Hemocue machine (like we will do today) and record your Haemoglobin, weight, height, and the circumference of your upper arm. I will also enquire about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy. The dietary data assistant will also visit your twice around this time.

Your participation in this study will be complete after two visits from the nutrition assistant and three visits you to interview you have been completed.

Are there any risks if you participate?

Finger prick blood tests can be a little uncomfortable but there is minimal risk associated with them and we will follow all best practices of hygiene and infection control.

We do not think that any harm will come to you, but it is possible that you might find sharing information about your pregnancy uncomfortable or upsetting. You don't have to continue to take part if you don't feel like it. If you would like to talk to someone about the feelings generated by the questions, please contact a member of HERD staff.

Are there any benefits if you participate?

Participating in this study will help you know the level of haemoglobin in your body and find out whether you have anaemia or not. You will also know about your weight, height and mid arm circumference status which will help you understand about your nutritional health. Knowing that you are pregnant at an early stage will help you plan your pregnancy, seek timely and appropriate health care for your unborn baby and eat nutritious food required for proper growth of your baby.

You will receive two home visits from trained individuals who will provide you iron folic acid tablets as per your anaemia status and discuss with you and your family about nutrition in pregnancy to prevent anaemia. You and your family members may benefit from participating in the monthly women's group meetings,

which can be informative and enjoyable. If we find that you have severe anaemia, we will alert you to get medical assistance from the suitable health facility.

At the end of your last interview, we undertake with you at around 30 weeks' gestation you will receive Rs 1000 as a thank you for giving up your time to take part in the study.

Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential. Only researchers directly associated with this project, who are involved in finding you to measure/interview you, will have access to your name and address. All other researchers who look at the information you share with us will not be able to identify you as your name and address will be removed. You will be allocated a trial participant card with a unique number, which will be used as a code to identify you instead of your name. You will not be able to be identified in any ensuing reports or publications.

If you consent to take part in this study, the records obtained while you are in this study (age, ethnicity, religion, education, haemoglobin concentration, measurements, symptoms of illness and so on) will remain strictly confidential at all times. The information will be held securely on either paper or electronically at HERD International and in University College London in the UK under the provisions the local Data Protection laws. Your name will not be passed to anyone else outside the research team who is not involved in the trial. Your records will be available to people authorised to work on the trial and those responsible for ensuring that the study is carried out correctly. Also, your name and address will be shared with the health facility to inform them regarding your IFA intake from CAPPT project in order to prevent duplication of iron tablet consumption. By signing the consent form, you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study. Further research might involve other researchers using the information you give us, but without your name attached to it. Alternatively, we or other researchers might seek to find you in the future to undertake further research with you.

If you withdraw consent from further study, unless you object, your data and samples will remain on file and will be included in the final study analysis.

In line with Nepal and UK regulations, at the end of the study your data will be securely archived in UK and in Nepal.

What will happen to the results of the research project?

The results of the study will be available after it finishes and will be published in a scientific journal and presented at a scientific conference. The data will be anonymous and none of the participants in the trial will be identified in any report or publication. You will be able to see the study results (no personal information revealed) from a website that we will set up for this project.

Data Protection Privacy Notice

The data controller for this project will be University College London (UCL) and HERD International together. The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data and can be contacted at data-protection@ucl.ac.uk.

Ethical approval

This study has been approved by the Nepal Health Research Council Approval ID number 353/2019, UCL Research Ethics Committee: Project ID number: 14301/001 and London School of Hygiene and Tropical Medicine ethics committee ID number: 16528.

Agreeing to take part

Your participation is voluntary. If you don't want to take part, you can refuse without giving a reason. If you decide to take part in the menstrual monitoring, you will be given this information sheet to keep and be asked to sign or thumb print the consent. If you agree to participate and then change your mind at any time,

please tell us and we will stop visiting you. We will take a photo of the consent form with your signature which will be filed in your records. You can have more time to think this over if you are at all unsure.

Contact for further information

You are encouraged to ask any questions you wish, before, during or after getting involved. If you have any questions about the study, please speak to the HERD International researchers who visit you, who will be able to provide you with up-to-date information about the procedure(s) and supplements/ medicines involved. If you require any further information or have any concerns while taking part in the study, you can contact:

Trial Manager, HERD International, Prasuti Griha Marg, Thapathali, Kathmandu. Tel 01-4238045

or

Dr Naomi Saville, Senior Research Associate, University College London Institute for Global Health and Technical advisor to HERD, Kathmandu Nepal. Tel: 01-4238045

HERD International District Office, Taulihawa, Kapilbastu. Tel: number: 076-590090

Thank you for reading this information sheet and for considering whether to take part in this research study.

Supplementary Annex 4: Full Trial participant information sheets in English

a) Control arm Participants

Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Participant Information Sheet for Pregnant Women in Control Arm

Introduction

Namaste! My name is _____. I have come from HERD International located in Thapathali, Kathmandu. HERD International is a national level research organization. This organization has been conducting various programmes and research in the health, environment, and social development. Currently, HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women in Kapilbastu. I would like to invite you to be a part of this study.

Before you decide whether to participate, it is important for you to understand why this research is being done and what participation will involve. I will read what is written in this information sheet aloud to you. You can ask me if there is anything that you do not understand or if you want more information. You will be given a copy of this information sheet. Take your time to decide whether or not you want to take part in the study or not. Thank you for reading this/listening to me.

Details of the study

HERD International in partnership with University College London is conducting a study with an aim to reduce anaemia in pregnant women. The Medical Research Council (UK) is funding this research.
Anaemia is a condition when there is decreased haemoglobin in blood, and this is caused by various factors. In Nepal, lack of iron is the most common cause of anaemia in pregnancy. It is important to reduce anaemia in pregnancy because low iron levels are associated with illness and complications during pregnancy and childbirth. Pregnant women who are anaemic are much more likely to die during childbirth than those women who are not and their infants are more likely to be born small for gestational age.
In Nepal, Kapilbastu is one of the districts where anaemia is highly prevalent. Hence, we have chosen 54 clusters (103 old-wards) within 9 pallikas of Kapilbastu for this study. We are involving approximately 1054 pregnant women residing within these 54 clusters. These 54 clusters will be divided equally into 2 groups, each group comprising of 27 clusters and more than 500 pregnant women.
This research is designed to find out how anaemia in pregnant women can be reduced in this community by doing the following:

a. Visiting the home of pregnant women by HERD staff to test their Haemoglobin levels and provide tailored iron-folic acid (IFA) tablets as per their anaemia status and nutrition counselling.

b. Mobilizing women's groups to discuss anaemia, supplements, diet, and antenatal care in pregnancy using Participatory Learning and Action (PLA) method.

Who are we inviting to participate?

You can take part in this research if you are a married woman or girl aged 13 to 49 years, pregnant at less than 20 weeks of gestation, planning to live in this study area for most of your pregnancy and are able to respond to the survey questions.

What will happen if you agree to take part in this study?

If you decide to take part and give your consent (by signing or thumb-printing a consent form), first I will give you a trial participant card with a unique identification number which will be your ID for this study period. I request you to keep this id card in a safe place so that when my other colleagues come to visit you, you can show them this card. You can also show this at the health facility to show the health worker that you are involved in the study. On a tablet, I will record some personal details about you such as your age, education, household details, medical and obstetric history. Also, today I will do a finger prick to obtain blood to test

your Haemoglobin level using a Hemocue machine to check whether you have anaemia or not. I will also measure and record your weight, height, the circumference of your upper arm and ask you some questions about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy.

I will visit you again at around 30 weeks' gestation and measure and record your Haemoglobin, weight, height, and the circumference of your upper arm. I will also enquire about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy.

Another HERD staff (dietary data assistant) may also visit you and your family at around 30 weeks' gestation and again within the same week to ask you and your husband (or another male family member) in detail about what you ate the day before.

We will visit you again at 30 weeks of gestation and measure your haemoglobin level with a Hemocue machine (like we will do today) and record your Haemoglobin, weight, height, and the circumference of your upper arm. I will also enquire about your eating habits, iron supplements, antenatal care, and any illness/discomfort you may have during pregnancy. The dietary data assistant will also visit your twice around this time.

Your participation in this study will be complete after all three visits you to interview you have been completed.

Are there any risks if you participate?

Finger prick blood tests can be a little uncomfortable but there is minimal risk associated with them and we will follow all best practices of hygiene and infection control.

We do not think that any harm will come to you, but it is possible that you might find sharing information about your pregnancy uncomfortable or upsetting. You don't have to continue to take part if you don't feel like it. If you would like to talk to someone about the feelings generated by the questions, please contact a member of HERD staff.

Are there any benefits if you participate?

Participating in this study will help you know the level of haemoglobin in your body and find out whether you have anaemia or not. You will also know about your weight, height and mid arm circumference status which will help you understand about your nutritional health. Knowing that you are pregnant at an early stage will help you plan your pregnancy, seek timely and appropriate health care for your unborn baby and eat nutritious food required for proper growth of your baby.

At the end of your last interview, we undertake with you at around 30 weeks' gestation you will receive Rs 1000 as a thank you for giving up your time to take part in the study.

Will my taking part in this project be kept confidential?

All the information that we collect about you during the course of the research will be kept strictly confidential. Only researchers directly associated with this project, who are involved in finding you to measure/interview you, will have access to your name and address. All other researchers who look at the information you share with us will not be able to identify you as your name and address will be removed. You will be allocated a trial participant card with a unique number, which will be used as a code to identify you instead of your name. You will not be able to be identified in any ensuing reports or publications.

If you consent to take part in this study, the records obtained while you are in this study (age, ethnicity, religion, education, haemoglobin concentration, measurements, symptoms of illness and so on) will remain strictly confidential at all times. The information will be held securely on either paper or electronically at HERD International and in University College London in the UK under the provisions the local Data Protection laws. Your name will not be passed to anyone else outside the research team who is not involved in the trial. Your records will be available to people authorised to work on the trial and those responsible for ensuring

that the study is carried out correctly. By signing the consent form, you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study. Further research might involve other researchers using the information you give us, but without your name attached to it. Alternatively, we or other researchers might seek to find you in the future to undertake further research with you.

If you withdraw consent from further study, unless you object, your data and samples will remain on file and will be included in the final study analysis.

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HERD International District Office, Taulihawa, Kapilbastu. Tel: number: 076-590090

Thank you for reading this information sheet and for considering whether to take part in this research study.

b) Intervention arm participants

Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Participant Information Sheet for Pregnant Women Intervention Arm

Introduction

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What will happen if you agree to take part in this study?

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The nutrition assistant will also invite you and your family members to attend monthly participatory women's groups (PLA meetings), which will be held in your community. You can attend these with a family member or a friend if you would like. The groups are open to anyone in the community. The nutrition assistant from HERD and your FCHV will facilitate these meetings and will discuss the problem of anaemia in pregnancy and how to reduce it through improved diet, eating iron-folic acid (IFA) tablets and going for antenatal care.

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Are there any risks if you participate?

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HERD International District Office, Taulihawa, Kapilbastu. Tel: number: 076-590090

Thank you for reading this information sheet and for considering whether to take part in this research study.

Supplementary Annex 5: Menstrual monitoring consent form in English

Patient Identification Number for this trial:

CONSENT FORM FOR MENSTRUAL MONITORING
Title of Study: Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Name and Contact Details of the Researcher(s):
DR SUSHIL BARAL 9851068940 and DR NAOMI SAVILLE 9851017232

This study has been approved by the Nepal Health Research Council Approval ID number 353/2019, UCL Research Ethics Committee: Project ID number: 14301/001 and London School of Hygiene and Tropical Medicine ethics committee ID number: 16528.

Thank you for considering taking part in this research. The researcher who has come to your home must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research. If you have any questions arising from the Information Sheet or explanation already given, please ask the researcher before you decide to participate in this study. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box below I am consenting to this element of the study.

In case of the married girl of age 14 to 19 running years (13 to 18 completed years), take the consent from her guardians as well. This means filling the tick box columns with the participant and *her guardian and getting the signature or thumb print of both of them.*

	Woman's Tick Box	Guardian's Tick box
I confirm that I have read the Information Sheet for the above study (or it has been read to me in an appropriate language) and I understood its content.		
I have had an opportunity to consider the information and what will be expected of me and to ask questions which have been answered to my satisfaction.		
I understand that my participation in this research is completely voluntary. I understand that I am free to withdraw from the research at any time without any repercussions. I understand that I can halt an interview at any point if I feel uncomfortable.		
I understand the potential risks of participating and the support that will be available to me should I become distressed during the course of the research.		
I understand that I will not benefit financially from this study or from any possible outcome it may result in in the future.		

I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified by anyone, except those who are involved in meeting me to take measurements and ask questions.		
I understand that the data will not be made available to any commercial organisations but are solely the responsibility of the researcher(s) undertaking this study.		
I understand that my data gathered in this study will be securely stored anonymously (without my name and address) and that it will not be possible to identify me in any publications.		
I understand that my personal information and my data will not be possible to identify me in any publications.		
I agree that my anonymised research data (that has my name and address removed) may be used by others for future research. I understand that no one will be able to identify you me if/when this these data are shared.		
I would be happy for the data I provide, including my name and address, to be archived in the UCL Data Safe Haven to be kept there, and other secure locations in Nepal and UK, in case researchers need to find me again in the future. I understand that these personally identifiable data will not be available to anyone except authorised researchers who need my name and address to find me again in the future.		
I understand that when I consent to have my photos taken while engaging in the research activities during the research period, that these could be published on HERD international's or UCL's website or other publications.		
I would be happy to be contacted in future by HERD International and/or UCL researchers who would like to invite me to participate in follow-up studies to this project (for example if someone came to measure me or my child after this study ended) .		
I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.		
I consent to participate in this study		

Signing this document means that you voluntarily agree to participate in this research after understanding the information provided to you.

(In case the married participant's age is between 14 and 19 running years (13 -18 completed years)

_____	_____	_____
Name of guardian	Date	Signature

OR Guardian's Fingerprints	Left	Right

_____ _____ _____

Name of participant Date Signature

OR Participant's Fingerprints

Left	Right Left

_____ _____ _____

Researcher (Data Assistant) Date Signature

Supplementary Annex 6: Full Trial consent form in English

Study Number:
Patient Identification Number for this trial:

CONSENT FORM
Title of Study: Comprehensive Anaemia Program and Personalized Therapies (CAPPT) trial

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Name and Contact Details of the Researcher(s):
DR SUSHIL BARAL 9851068940 and DR NAOMI SAVILLE 9851017232

This study has been approved by the Nepal Health Research Council Approval ID number 353/2019, UCL Research Ethics Committee: Project ID number: 14301/001 and London School of Hygiene and Tropical Medicine ethics committee ID number: 16528.

Thank you for considering taking part in this research. The researcher who has come to your home must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by ticking/initialling each box below I am consenting to this element of the study. I understand that it will be assumed that unticked boxes means that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element that I may be deemed ineligible for the study.

In case of the married girl of age 14 to 19 running years (13 to 18 completed years), take the consent from her guardians as well. This means filling the tick box columns with the participant and *her guardian and getting the signature or thumb print of both of them.*

	Pregnant woman's Tick Box	Guardian's Tick box
I confirm that I have read the Information Sheet for the above study (or it has been read to me in an appropriate language) and I understood its content.		
I have had an opportunity to consider the information and what will be expected of me and to ask questions which have been answered to my satisfaction.		
I understand that my participation in this research is completely voluntary. I understand that I am free to withdraw from the research at any time without any repercussions. I understand that I can halt an interview at any point if I feel uncomfortable.		
I understand the potential risks of participating and the support that will be available to me should I become distressed during the course of the research.		
I understand that I will not benefit financially from this study or from any possible outcome it may result in in the future.		
I understand that my personal information *(including ethnicity, age, socio-economic and educational status, past medical and obstetric history)* will be used when analysing the data, but not my name.		
I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified by anyone, except those who are involved in meeting me to take measurements and ask questions.		

I understand that my data gathered in this study will be securely stored anonymously (without my name and address) and that it will not be possible to identify me in any publications.		
I understand that the data will not be made available to any commercial organisations but are solely the responsibility of the researcher(s) undertaking this study.		
I agree that my anonymised research data (that has my name and address removed) may be used by others for future research. I understand that no one will be able to identify you me if/when this these data are shared.		
I would be happy for the data I provide, including my name and address, to be archived in the UCL Data Safe Haven to be kept there, and other secure locations in Nepal and UK, in case researchers need to find me again in the future. I understand that these personally identifiable data will not be available to anyone except authorised researchers who need my name and address to find me again in the future.		
I understand that when I consent to have my photos taken while engaging in the research activities during the research period, that these could be published on HERD international's or UCL's website or other publications.		
I would be happy to be contacted in future by HERD International and/or UCL researchers who would like to invite me to participate in follow-up studies to this project (for example if someone came to measure me or my child after this study ended) .		
I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.		
I consent to participate in this study		

Phone no for future contact:

Signing this document means that you voluntarily agree to participate in this research after understanding the information provided to you.

(In case the married participant's age is between 14 and 19 running years (13 -18 completed years)

_____ _____ _____

Name of guardian Date Signature

OR Guardian's Finger Prints

Left	Right

_____ _____ _____

Name of participant Date Signature

OR Participant's
Finger Prints

Left	Right Left

_____ _____ _____

Researcher (Data Assistant) Date Signature

Supplementary Annex 7. Expected pregnancies to be enrolled and numbers after loss to follow-up

Number of pregnancies enrolled and measured in run-in period and full trial							
		Before loss to follow-up			After loss to follow-up of 20%		
No of clusters per arm	% <20 weeks	Run-in period of 1 month	Full trial enrolment of 6 months	Total across the trial	Run-in period of 1 month	**Full trial enrolment of 6 months**[1]	Total across the trial
Estimates per cluster	50%	3.3	19.5	22.8	2.6	**15.6**	18.2
	33%	2.2	13.0	15.2	1.7	**10.4**	12.1
Estimates per arm	50%	88	527	614	70	**421**	491
	33%	59	351	410	47	**281**	328
Estimates for whole trial	50%	176	1054	1229	140	**842**	983
	33%	117	702	819	94	**562**	655

[1] number per cluster used in power calculation are given in this column. The power calculation assumes detectable difference of 0.4g/dl Hb, ICC (rho) 0.09, coefficient of variation of cluster size 0.27, 27 clusters per arm and SDs of 1.2 or 1.25

CAPPT
Trial Steering Committee Charter

[Comprehensive Anaemia Program and Personalised Therapies Trial]

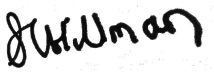
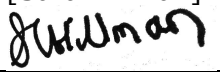
Two sister non blinded cluster randomized controlled trials conducted in rural areas in Nepal and India

ISRCTN to be completed

Trial Steering Committee Charter

Version 2, Date 24.02.2020

(developed using MRC Clinical Trials Unit template TSC Charter version 1.02, 13-Mar-2006)

Authorised by:			
Name:	[Sara Hillman]	Role:	[Chief Investigator]
Signature:		Date:	23-12-2019
Prepared by			
Name:	[Sara Hillman]	Role:	[Chief Investigator]
Signature:		Date:	23-12-2019

CONTENT	DETAILS OF TSC
Name (& Sponsor's ID) of trial	All India Institute Medical Sciences, New Delhi and HERD, Nepal Trial registration: to be completed
Objectives of trial, including interventions being investigated	The primary objective of the CAPPT trial is to assess if providing a tailored dosage of oral iron-folic acid (IFA) supplementation along with a personalized package of nutrition education and counselling (the home visiting intervention) supported by community-based participatory learning and action (PLA) women's groups increases haemoglobin (Hb) levels at 28 weeks of pregnancy, compared with haemoglobin levels in women who have PLA women's groups only in their communities (PLA plus routine care) and with women who have access to routine antenatal care only (control). Secondary objectives are as follows: 1. Identify whether a tailored home-visiting intervention supported by PLA women's groups and/or PLA women's groups alone improve the following by 28 weeks gestation: Pregnant Women's (PWs) dietary diversity and average daily intake of key micronutrients; equity of food and nutrient allocation between PW and their husbands; and compliance with recommended intake of prescribed supplements 2. Assess if any increases in haemoglobin (Hb) and secondary outcomes at 28 weeks are sustained or improved by 34 weeks gestation. 3. Identify the reported symptoms/side effects of iron supplements in groups according to dosage. 4. Evaluate who benefits most from the intervention. 6. Conduct a process evaluation to explore the mechanisms of effect and describe the context and implementation of the intervention 7. Conduct an economic evaluation to assess if the intervention is cost-effective, and what it costs to deliver at scale.
Outline of scope of Charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Trial Steering Committee (TSC) for this trial, including the timing of meetings, methods of providing information to and from the TSC, frequency and format of meetings and relationships with other trial committees.
2. ROLES AND RESPONSIBILITIES	
A broad statement of the aims of the TSC	To act as the oversight body for this trial on behalf of the Sponsor/Funder.
Terms of reference	The role of the TSC is to provide oversight for the trial. It should also provide advice through its independent Chair to the Trial Management Group (TMG), MRC, any other Funder on all aspects of the trial.
Specific roles of TSC	• provide expert oversight of the trial • maintain confidentiality of all trial information that is not already in the public domain • make decisions as to the future continuation (or otherwise) of the trial/s • monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems • approve the protocol(s)

CONTENT	DETAILS OF TSC
	• review regular reports of the trial from the Trial Management Group (TMG) • receive letters of feedback from the DMC and consider their recommendations • assess the impact and relevance of any accumulating external evidence • monitor follow-up rates and review strategies from TMG to deal with problems • censure sites that are deviating from the protocol • approve any amendments to the protocol, where appropriate • approve any proposals by the TMG concerning any change to the design of the trial, including additional sub studies • oversee the timely reporting of trial results • approve / comment on the statistical analysis plan • approve external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples
3. BEFORE OR EARLY IN THE TRIAL	
Whether the TSC will have input into the protocol	All potential independent TSC members should have opportunity to comment on the protocol as early as possible. Before recruitment begins the trial will have undergone review by the Sponsor/Funder (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential independent TSC member has major reservations about the trial (e.g. the protocol, the logistics, ethical concerns) they should report these to the Chief Investigator and may decide not to accept the invitation to join. TSC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Trial specific issues	
Any issues specific to the disease under study	Anaemia is a multi factorial problem and this trial is not designed to ameliorate anaemia other than that caused by iron deficiency and other micronutrients. This is a pragmatic trial and will use existing stock of iron/folate tablets in each country. There is a possibility of low supply.
Any specific regulatory issues	Consent and ascent issues have been discussed in detail with local ethics committees in each country. In Nepal, we will be recruiting women from the age of 13 and this has been approached with particular sensitivity and advice from the Nepal Research Ethics Committee.
Any other issues specific to the treatment under study	None immediately apparent
Whether members of the TSC will have a contract	TSC members will not be asked to formally sign a contract but should formally register their agreement to join the group by confirming (1) that they agree to be a member of the TSC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time. Members should complete and return the form in Annexes 1 or 2. Any observers (attendees who are not members) will sign a confidentiality agreement on the first occasion they attend a meeting (Annexe 3).

CONTENT	DETAILS OF TSC
4. COMPOSITION	
Membership and size of the TSC	The majority of members of the TSC, including the Chair, should be independent [1]of the trial (see section 5). Non-independent members will also be part of the TSC. The members of the TSC for this trial are: (1) *Professor Peter Brocklehurst – Independent member and chair of the Trial Steering Committee* (2) *Dr Kevin Kao – Independent member haematology (red cell) expert* (3) *Dr Shalini Singh – Independent member maternal health expert* (4) *Dr Madhu Devkota – Independent member – nutrition expert* (5) *Dr Umesh Kapil-Expert member from India – nutrition specialist* (6) *Dr Sara Hillman – Chief Investigator*
The Chair, how they are chosen and the Chair's role.	The Chair should have previous experience of serving on trial committees and experience of Chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area would be beneficial
The responsibilities of the CI and other members of the TMG	The CI (and, if appropriate, other TMG members) is an important member of the TSC and no major decisions should be made without their involvement.
The responsibilities of the observers	Additional observers may be in attendance through (parts of) the TSC meetings in order to provide input on behalf of the trial's Sponsor/Funder or to provide specific relevant expertise.
5. RELATIONSHIPS	
Relationships with Chief Investigators, other trial committees (e.g. TMG and DMC), Sponsor/Funder and regulatory bodies	The responsibilities of each trial committee are detailed in the protocol and in the respective Charters.
Advisory and executive bodies	The TSC is the oversight body and is delegated the roles in Section 2 by the Sponsor. All substantial issues regarding the trial must go to the TSC for consideration. The IDMC is advisory to the TSC.
Payments to TSC members	Members will be reimbursed for reasonable travel costs in country to attend meetings in person. No other payments or rewards would be given to professional members.
The need for TSC members to disclose information about any real or potential competing interests	Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility (See Annex 1). TSC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to

[1] Independence is defined in Table 1 of Annexe 1

CONTENT	DETAILS OF TSC
	trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting.
6. ORGANISATION OF MEETINGS	
Expected frequency of TSC meetings	The TSC will meet at least yearly. At the request of the TSC, interim meetings, in person or by teleconference, will be organised. Many/major trial issues may need to be dealt with between meetings, by phone or by email. TSC members should be prepared for such instances.
Attendance of TSC members at meetings	Effort will be made for all members to attend. The Chief Investigator will work for a date that enables this. It is accepted that the CI may not attend all meetings where major actions are not expected. Members who cannot attend in person should be encouraged to participate by teleconference. If, at short notice, any TSC members cannot attend then the TSC may still meet if at least two independent members, including the Chair (unless otherwise agreed), will be present as well as a representative of the trial team. If the TSC is considering a major action after such a meeting the TSC Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full TSC.
How TSC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Presence will be usually limited to the TSC members, observers from the Sponsor/Funder, trials unit and the Facilitator. Other attendees may be invited for all or part of the meeting by the TSC including the trial statistician. The observers are not members of the TSC but may be invited to provide expert input or to represent the funding bodies involved; other observers will be at the discretion of the TSC and the Chief Investigator but may include members of the TMG other than the CI.
Can TSC members who cannot attend the meeting input	If the report is circulated before the meeting, TSC members who will not be able to attend the meeting may pass comments to the TSC Chair, for contact for consideration during the discussions.
What happens to independent members who do not attend meetings	If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they should be asked if they wish to remain part of the TSC. If an independent member does not attend a third meeting, strong consideration should be given to replacing this member.
7. TRIAL DOCUMENTATION AND PROCEDURES TO ENSURE CONFIDENTIALITY AND PROPER COMMUNICATION	
Intended content of material to be considered during meetings	A short report will be prepared by members from each country team. This will report on accrual and any matters affecting the trial. Additionally, the material may include a report *from* the DMC, requests *from* the TMG or draft publications. No trial outcome measure data will be presented by arm unless explicitly authorised by the DMC (eg toxicity). Where relevant, accrual, compliance with follow-up and adherence to treatment may be presented by centre.
Whether reports to the TSC be available before the meeting or only at/during the meeting	It is usually helpful for the TSC to receive the report at least 1 week and preferably at least 2 weeks before any meetings. Different procedures may apply to teleconference meetings.

CONTENT	DETAILS OF TSC
The people who will see the accumulating data and interim analysis by randomised group	The accumulating trial data by arm and interim analyses will be confidential. These will be viewed only by the DMC. The TSC will not be routinely privy to these interim reports. The DMC will make recommendations to the TSC based on the interim data.
Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the TSC members; it is a responsibility of the TMG. However, the TSC should continue to be made aware of other data that may impact on a trial.
To whom the TSC will communicate the decisions that are made	(See Section 9)
What will happen to the papers after the meeting	TSC members would be expected to delete, destroy or store securely copies of the reports to and from the TSC, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential. The Chief Investigator will keep a central record of all minutes, reports and correspondence by the TSC.
8. DECISION MAKING	
What decisions will be open to the TSC	Based on recommendations from the DMC, possible decisions include:- • No action needed, trial continues as planned • Early stopping due, for example, to clear benefit or harm of a treatment, futility or external evidence • Modifying target recruitment, or pre-analysis follow-up, based on any change to the assumptions underlying the original trial sample size calculation (but not on any emerging differences) • Stopping one or more arms of a multi-arm trial • Sanctioning and/or proposing protocol changes Based on other factors, possible decisions include the decisions above and: • Approving proposed protocol amendments or new trial sub-studies • Approving requests for early release of (subsets of) data • Approving external applications for the use of stored samples • Approving presentation of results during the trial or soon after closure • Approval of new centres or strategies to improve recruitment or follow-up
The role of formal statistical methods	Formal statistical methods may have been considered by the DMC in making their recommendations to the TSC. These methods are usually used as guidelines rather than absolute rules. This is because they generally only consider one dimension of the trial. The DMC will record reasons for disregarding a stopping guideline in the notes of their meetings and may choose to also note this in their report to the TSC if necessary.

CONTENT	DETAILS OF TSC
How decisions or recommendations will be reached within the TSC	Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any decision is made.
When the TSC is quorate for decision-making	At least two independent members of the TSC should be present including the Chair, plus a representative of the and, if major action is to be considered, the CI.
9. REPORTING	
To whom will the TSC report their recommendations/decisions, and in what form	The TSC will report their decisions to the TMG who will be responsible for implementing any actions resulting. The TSC may also provide feedback to the IDMC and, where appropriate, to the Sponsor/Funder. Copies of communications will pass through the Chief Investigator. Communications will be expected to be received by parties within 28 working days.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Notes of key points and actions will be made by the Rapporteur for the trial. This will include details of whether potential competing interests have changed for any attendees since the previous meeting. The draft minutes will be initially circulated for comment to those TSC members who were present at the meeting. The TSC Chair will sign off the final version of minutes or notes.
What will be done if there is disagreement between the TSC and other trial committees	The TSC is the oversight body for the trial. However, the TSC should have good reason before deciding not to accept requests from the TMG and recommendations from the DMC. If there are serious problems or concerns with the TSC decision following an DMC recommendation, a joint meeting of the TSC and DMC should be held. The information to be shown would depend upon the action proposed and each committees' concerns. Depending on the reason for the disagreement confidential data and/or data by trial arm may have to be revealed to all or some of those attending such a meeting: this would be minimised where possible. The meeting would be Chaired by a senior member of the UCL CTU staff or an external expert who is not directly involved with the trial.
10. AFTER THE TRIAL	
Publication of results	The TSC will oversee the timely analysis, writing up and publication of the main trial results. The independent members of the TSC will have the opportunity to read and comment on the proposed main publications of trial data prior to submission. This review may be concurrent to that of the trial investigators and IDMC.
The information about the TSC that will be included in published trial reports	TSC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.
Any constraints on TSC members divulging information about their deliberations after the trial has been published	

Abbreviations and glossary

CI	Chief Investigator
DMC	Data Monitoring Committee

DMC	Data Monitoring Committee
ISRCTN	International standard randomised controlled trial number
MRC	Medical Research Council
PW	Pregnant Woman
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UARTMG	Unexpected adverse reactionTrial Management Group
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction

Annexe 1: Agreement and competing interests form for independent members

CAAPT Trial Steering Committee: Agreement to join the Trial Steering Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the TSC Facilitator.

(please initial box to agree)

	I have read and understood the TSC Charter version V1, dated 23/12/2019
	I agree to join the Trial Steering Committee for this trial as an independent member
	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TSC may be biased in some fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Potential competing interests should be disclosed. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. **Table 1** lists potential competing interests.

	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial

- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Note: This TSC charter was developed using MRC CTU template TSC Charter version 1.02, 13-Mar-2006

Annexe 2: Agreement and competing interests form for non-independent members

CAAPT Trial Steering Committee: Agreement to join the Trial Steering Committee as an non-independent member and disclosure of potential competing interests

Please complete the following document and return to the Facilitator.

(please initial box to agree)

	I have read and understood the TSC Charter version V1, dated23/12/2019
	I agree to join the Trial Steering Committee for this trial as an non-independent member
	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a TSC may be biased in some undisclosed fashion is important for the credibility of the decisions made by the TSC and for the integrity of the trial.

Possible competing interests should be disclosed. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TSC member should remove the conflict or stop participating in the TSC. **Table 1** lists potential competing interests.

	No, I have no competing interests to declare other than involvement in the trial
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention

- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products

Note: This TSC charter was developed using MRC CTU template TSC Charter version 1.02, 13-Mar-2006

Annexe 3: Agreement and confidentiality agreement for observers

CAPPT Trial Steering Committee: Agreement to attend the Trial Steering Committee and treat all information confidentially

Please complete the following document and return to the Facilitator.

(please initial box to agree)

	I have received a copy of the TSC Charter version 1, 23/12/19
	I agree to attend the Trial Steering Committee meeting on ___/____/_____
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

Note: This TSC charter was developed using MRC CTU template TSC Charter version 1.02, 13-Mar-2006

Annexe 4: Summarise changes from previous version

Version 1.0
This is version 1.0 of the TSC charter for this trial. There are no changes to be reported.

Supplementary Annex 9: Data Monitoring Committee (DMC) charter

CAPPT Trial
Comprehensive Anaemia Programme and Personalized Therapies

DATA MONITORING COMMITTEE CHARTER

Study Title	Cluster randomized controlled trial of a home counselling (and PLA in Nepal only) intervention to improve anaemia in pregnant women in rural India and Nepal
Short Study Name	CAPPT
Trial registration	ISRCTN registration number: 12272130
Ethical approval	Ethical approval has been obtained from UCL ethics committee (Project ID number: 14301/001), Nepal Heath Research Council (NHRC approval number: 353/2019) AIIMS Hospital Committee and London School of Hygiene and Tropical Medicine ethics committee (approval number: 16528).
Sponsors	AIIMS and HERD
Version of the Document	2
Date of the current version	24 May 2021

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1. TRIAL OVERVIEW

The aim is to improve maternal nutrition and prevent iron deficiency anaemia in pregnancy. The primary objective of the CAPPT trial is to assess, if providing a tailored dosage of oral iron- folic acid (IFA) supplements along with a personalized package of nutrition education and counselling (the home visiting intervention) supported by community-based participatory learning and action (PLA) women's groups, increases haemoglobin (Hb) levels at 30 weeks of pregnancy, compared with haemoglobin (Hb) levels in women who have access to routine antenatal care only (control).

In Nepal the trial will include two arms:

1) Control (routine care) arm where women have access to usual government services.

2) 'Home visiting' intervention arm comprising of a home-based counselling with tailored iron/folic acid supplementation and participatory learning and action women's groups (PLA) held in the community for pregnant and non-pregnant women to attend in addition to routine care. During two home visits, the nutrition assistant tests the pregnant woman's haemoglobin level and asks her about her diet and barriers to good nutrition. Then she provides a tailored dose of iron-folic acid tablets as well as counselling on how to improve diet.

In India no PLA will be offered and the study will comprise of two arms:

1) Control (routine care) arm

2) 'Home visiting' intervention arm comprising of a home-based counselling with tailored iron/folic acid supplementation with very similar content in both sites

The study is a non-blinded cluster-randomised controlled trial.

Study partners: The study activities are being led jointly by HERD in Nepal and All India Institute Medical Sciences (AIIMS, New Delhi. Funding for Nepal and UK budget through the MRC and in India from the Department of biotechnology (DBT).

2. OUTLINE AND SCOPE OF DMC CHARTER

The purpose of this document is to describe the roles and responsibilities of the independent DMC for the CAPPT trial, including the timing and format of meetings, methods of providing information to and from the DMC, and relationships with other committees. The Charter was prepared using the recommendations of the DAMOCLES group[2].

3. ROLE OF DMC

The role of the DMC is to:

- Protect and serve the CAPPT trial participants and to assist and advise the Principal Investigators so as to protect the validity and credibility of the trial.

- Safeguard the interests of the trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the trial.

The DMC will review the progress and data of this trial during an interim and final meeting and provide advice on its conduct to the Trial Steering Committee. After the final meeting, the DMC should inform the Chair of the Steering Committee if, in their view, the results are likely to convince a broad range of public health practitioners and researchers, that on balance one trial arm is clearly indicated or contraindicated, such that this evidence should inform current policy and practice.

4. SPECIFIC CHARGES TO THE DMC IN THE CAPPT TRIAL

The DMC will review the trial's interim and final data, including figures on recruitment, data quality, and main outcome data. The charges to the DMC are to:

1. Monitor recruitment figures and loss to follow-up
2. Assess data quality, including completeness
3. Monitor compliance with the protocol by investigators
4. Monitor evidence for differences in the outcome measures, by arm
5. Decide whether to recommend that the trial should continue to recruit participants, or whether recruitment should be terminated early
6. Suggest additional data analyses if necessary
7. Advise on protocol modifications suggested by investigators or sponsors (e.g., recruitment length)
8. Monitor planned sample size assumption
9. Review the analysis plan for final trial analyses in due course
10. Monitor compliance with the interim DMC recommendations in the final DMC meeting

It is important for DMC members to read the trial protocol before participating in meetings. DMC members should be independent and constructively critical of the ongoing trial, but also supportive of its aims and methods. Any DMC members who wish to register a competing interest should inform one of the Principal Investigators (sara.hillman@ucl.ac.uk) prior to the first DMC meeting. Competing interests are not restricted to financial matters – involvement in other trials or intellectual investment are relevant. Although members will often be able to act objectively despite such connections, complete disclosure enhances credibility.

5. DMC COMPOSITION AND INDIVIDUAL RESPONSIBILITIES

[2] DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them do to their job well. *Lancet* 2005; **365**: 711-22.

The members of the DMC for the CAPPT trial are:

• Chair: Professor Keith West, Program Director, Human Nutrition Johns Hopkins University USA

• Mr James Martin, Institute of Applied Health Research, Research Fellow Institute of Applied Health Research, University of Birmingham, Birmingham, B15 2TT, UK j.t.martin@bham.ac.uk

• Dr. Rajendra Kumar BC -Research Advisor, Nepal Health Research Council, Kathmandu, Nepal. Research Team

member of Nepal Micronutrient Status Survey (2016). Email: drrajendra2005@gmail.com

• Dr Meghnath Dhimal, Chief / Senior Research Officer, Health Research Section,

Nepal Health Research Council, Kathmandu, Nepal. Email: meghdhimal@gmail.com

• Shobha Rao, Pune Maternal Nutrition Study

• Obstetric Haematologist- Dr Evangelia Koumoutsea Division of Hematology, Department of Medicine, Faculty of Medicine, University of Toronto. Email: evangelia.koumoutsea@uhn.ca

The investigators, trial advisory group and trial steering committee will be able to see data on the trial recruitment and follow-up combined across arms, data on the implementation of the intervention and data collection quality measures. They will not see the effect sizes for the primary outcome, which will only be seen by the DMC.

Team members from both sites will participate in the production of sections of the DMC report that present the trial recruitment and follow-up combined across arms, and the implementation of the intervention and data collection quality measures.

6. RELATIONSHIP WITH OTHER COMMITTEES

The CAPPT trial has two committees: a Trial Steering Committee (TSC) and a Data Monitoring Committee.

The role of the TSC is to:

1. Monitor and supervise the trial's progress towards its interim and overall objectives
2. Advise the funders (Medical Research Council, and DBT) on the conduct and presentation of all aspects of the trial

The DMC recommendations should be circulated in writing to the TSC, with copies marked to the Trial Statistician (A Copas) and one of the Co-PIs (Naomi Saville) The recommendations will be discussed in a formal TSC meeting shortly after the DMC meeting. The DMC makes recommendations to the Chair of the TSC (Professor Peter Brocklehurst p.brocklehurst@bham.ac.uk), who is responsible for final executive decisions (e.g., about stopping or continuing the trial, or modifying the protocol).

7. FREQUENCY AND FORMAT OF MEETINGS

The DMC will meet twice during the course of the trial: in December 2019 and towards the end of the trial (final DMC meeting). Because the DMC includes India , Nepal, Canadian and UK-based members, we will seek to have as many members as possible in a face-to-face meeting in Delhi or Kathmandu, but some members may only be able to join by teleconference and this will be accommodated.

8. DOCUMENTATION AND REPORTING

Materials to be made available to the DMC prior to the meeting include:

- The DMC Charter
- The CAPPT trial protocol
- A data report, also containing a meeting-specific list of charges to the DMC

The DMC recommendations, signed and dated by the Chair, should be circulated to the Trial Steering Committee Chair (Dr Peter Brocklehurst p.brocklehurst@bham.ac.uk), the Trial Statistician (a.copas@ucl.ac.uk) and one of the two co-

PIs (Dr Sara Hillman; sara.hillman@ucl.ac.uk and Dr Naomi Saville; n.saville@ucl.ac.uk) within three weeks of the meeting.

9. BLINDING AND CONFIDENTIALITY

DMC members will not be blind to allocation. The DMC members should not circulate the confidential data report to anyone outside the DMC. DMC members should destroy their reports after each meeting. Fresh copies of previous reports will be circulated before each meeting.

10. DECISION MAKING

Possible recommendations open to the DMC relating to each of the charges include:

- Satisfactory progress, no action needed, continue as planned
- Early stopping due, for example to:
  - (i) Serious problems in recruitment or retention.
  - (ii) Serious problems in implementing the intervention.
  - (iii) Serious error in the assumptions concerning the variability of the outcomes behind the sample size calculations (e.g., ICC).
  - (iv) A change in the environment of the trial which makes it no longer feasible or scientifically relevant (e.g., a change in government policy).
  - (v) Another trial reports results that make the trial redundant.
- Extending recruitment and/or extending follow-up
- Sanctioning and/or proposing protocol changes

Decision making methods should be proposed by the DMC Chair and agreed upon by all members at the first DMC meeting. In general, it is recommended that every effort should be made for the DMC to reach a unanimous decision. If this cannot be achieved, a vote may be taken. The role of the Chair is to summarise discussions and encourage consensus; it may be best for the Chair to give their own opinion last.

There should be a minimum of three attendees before the DMC is quorate for decision making. Members who cannot attend in person should be encouraged to attend by teleconference. If, at short notice, any DMC members cannot attend at all then the DMC may still meet if at least one statistician and one clinician, including the Chair, will be present. If the DMC is considering recommending major action after such a meeting the DMC chair should talk with the absent members as soon as possible after the meeting to check that they agree. If they do not, a teleconference should be arranged with the full DMC.

As the data report will be circulated before the meeting, DMC members who cannot attend may pass comments to the DMC Chair for consideration during the discussions. If a member is not able to attend the interim meeting, they should be asked if they wish to remain a part of the DMC. If not, they should be replaced.

If the DMC has serious concerns with the TSC decision, a meeting of these two groups should be held.

11. POST-TRIAL INTERACTIONS WITH THE DMC

The final DMC meeting will be an opportunity for the members to discuss and give their advice about data interpretation to the investigators. DMC members will be named, and their affiliations listed in the main trial publication, unless they request otherwise. Details of the timings and deliberations of the DMC meeting may be included in this publication, if required (e.g., because of extensions to recruitment/follow-up, or changes to the protocol).

12. EXPENSES RELATED TO DMC ATTENDANCE

While the trial team does not offer honorariums for participating in DMC meetings, we will meet any in country travel or telephone expenses incurred by the members in relation to meetings.

APPENDIX 1: Possible competing interests to be disclosed prior to DMC meetings

The avoidance of any perception that members of a DMC may be biased in some fashion is important for the

credibility of the decisions made by the Committee, and for the integrity of the trial as a whole. Possible competing interests should be disclosed to Dr Hillman and the Trial Statistician (Dr A Copas). In most cases, simple disclosure should be sufficient. Otherwise, the (potential) DMC member should remove the conflict or stop participating in the DMC. Below is a list of potential competing interests.

- Career tied up in a form of intervention assessed by the trial
- Hands-on participation in the trial
- Intellectual conflict, e.g., strong prior belief in or against the trial's experimental