Multiple Micronutrient Supplementation During Pregnancy (MMSDP): Efficacy Trials

by UNICEF / UNU / WHO Study Team

Report of a meeting held on March 4-8, 2002 at the Centre for International Child Health, Institute of Child Health, UCL, London, UK.

UCL

The child first and always

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Executive Summary

The high prevalence of low birth weight in infants in developing countries is a major health and development problem. Malnourished mothers are more likely to have low birth weight babies. Poor women tend to have diets that are micronutrient-poor, and many consume diets that inhibit micronutrient absorption, such that many women of reproductive age from developing countries suffer from multiple micronutrient deficiencies. The multiple micronutrient supplement agreed for use in trials at a UNICEF, WHO and UNU meeting in 1999, is now being used by research groups in trials funded by a variety of funding agencies. The research question being is whether multiple micronutrient supplements significantly improve pregnancy outcome, more so than iron-folate supplements. An interest was expressed to increase collaboration among the ongoing efficacy trials, and to that end a meeting was held at the Centre for International Child Health, Institute of Child Health, London, from March 4-8, 2002, funded by the Micronutrient Initiative. It was attended by leading researchers and principal investigators of multiple micronutreus trials, and policy-makers from several international agencies including DFID, UNICEF, UNU, WHO, the World Bank, CIDA, USAID, the Micronutrient Initiative and the Wellcome Trust. The principal investigators and representatives from UNICEF, WHO, UNU, and USAID spent the first four days of the meeting discussing the details of the trials. On the last day policy-makers from the World Bank, CIDA, the Wellcome Trust, and the Micronutrient Initiative joined in the discussion. The primary objectives of this meeting were:

- To maximise on the research outcomes from the various multiple micronutrient supplementation trials
- To ensure as far as possible improved comparability across various trials
- To maximise possibilities of pooling data across sites for a possible meta-analysis
- To discuss mechanisms by which research findings could be fast-tracked to policy-makers and programmes.

The efficacy trials under consideration included:

1. a study in Nepal looking at birth weight being conducted by CICH with funds from the Wellcome Trust;
2. a study in Guinea-Bissau looking at birth weight being conducted by the Royal Veterinary and Agricultural University with funds from DANIDA;
3. a study in Bangladesh looking at birth weight being conducted by ICDDRB with funds from UNICEF;
4. a study in Pakistan looking at birth weight being conducted by the Aga Khan University with funds from UNICEF;
5. a study in Indonesia looking at maternal mortality and birth weight being conducted by Helen Keller International with funds from UNICEF and USAID.

In addition, the group discussed three other protocols: a study in Bangladesh looking at vitamin A supplementation during pregnancy and maternal mortality being conducted by the Johns Hopkins' University group with funds from USAID and The Gates Foundation; a study in Tanzania looking at a different multiple micronutrient supplement during pregnancy and birth weight in non-HIV infected mothers being conducted by the Harvard School of Public Health group with funds from NIH and

UNICEF; a completed study from Nepal looking at a different multiple micronutrient supplement during pregnancy and birth weight and early child morality conducted by the Johns Hopkins University group with funds from UNICEF and USAID. After having jointly reviewed these protocols, the meeting split into two smaller working groups. The first group, consisting of the investigators, discussed further the design and ethical issues of efficacy trials and future collaboration. A second group considered the programme implications of the ongoing research.

A recommended list of minimum requirements for study design, outcomes to be measured, and confounders or effect-modifiers to be included was agreed, which will enhance the possibility of an eventual pooled analysis. It was agreed that whilst the use of birth weight as an outcome is important, it does not fully capture the potential benefits of improved maternal nutritional status on birth outcomes. All trials should seek to capture information on perinatal mortality. Other maternal mortality trials should also be considered. Collaboration across sites in the sharing of experience in developing standardized tools, such as verbal autopsy (abortion/miscarriage, stillbirth/neonatal death), and night blindness was initiated. All agreed on the desirability of developing local data safety and monitoring boards to manage the ongoing ethical aspects of such trials. Indonesia is most advanced in this and others would like to learn from them. Pathways to facilitate the process of policy change and enabling activities that could support the eventual distribution of multiple micronutrient supplements should they prove to be efficacious, within safer motherhood initiatives were also discussed, including the need for effectiveness trials to be run in parallel with the efficacy trials.

The group as a whole felt that the meeting had been very constructive and useful, and that continued efforts were called for to promote further collaboration across trial sites. Increased liaison was desirable for information sharing, keeping everybody updated, and even troubleshooting if necessary. A mailing list was suggested that should be expanded to include all constituents working on multiple micronutrient supplements, both efficacy and effectiveness studies, especially from developing countries. A further meeting was called for, which preferably should meet in South Asia within a year, to report on progress and involve an expanded set of research objectives and researchers and bring the necessary extra expertise onboard.

These findings and recommendations were presented to an expanded group of participants on the final day, which included representatives of Canadian CIDA, The Wellcome Trust Foundation, The World Bank, The Division of Reproductive Health of WHO, USAID, Helen Keller International and the Micronutrient Initiative. After discussion with this expanded group, it was largely agreed that the various organisations present could and should help support and carry forward the recommendations of the meeting.

Introduction

Whilst WHO recommends universal distribution of iron/folate supplements to anaemic mothers in developing countries, it is increasingly recognised that many such women suffer from multiple micronutrient deficiencies, not just iron deficiency. In recognition of this UNICEF, WHO and UNU have agreed upon the formulation of a multiple micronutrient supplement for use in trials with the view to eventually replacing the iron/folate supplement[1,2]. This supplement, the composition of which is described in Table 1, is being used by a variety of research groups in trials funded by a variety of funding agencies. The research question is whether multiple micronutrient supplements significantly improve pregnancy outcomes as compared to iron-folate supplements. An interest was expressed by both researchers and agencies involved to increase collaboration among the ongoing efficacy trials, and to that end a meeting was held at the Centre for International Child Health, Institute of Child Health, London, from March 4-8, 2002, funded by the Micronutrient Initiative.

The objectives of the meeting were directed towards both increasing the efficiency of the research effort and speeding the translation of scientific results into policy and programmes. Whilst the main aim of the meeting was to explore ways of increasing the collaboration across these research groups, great pains were taken to try to ensure that the discussions were firmly grounded in the needs and reality of intervention programmes. The meeting was attended by leading researchers and principal investigators of micronutrient trials, and policy-makers from several international agencies including UNICEF, UNU, WHO, HKI, the World Bank, CIDA, USAID, the Micronutrient Initiative and the Wellcome Trust. The first objective was to explore how to maximize the research outcomes that would be obtained from the various multiple micronutrient supplementation trials. The second objective was to seek ways of ensuring as far as possible improved comparability across the various trials, and if appropriate to maximize possibilities of pooling data across sites in the future. The third objective was to discuss mechanisms by which research findings would be fast-tracked to policy-makers and programmes as soon as results became available.

Table 1. Composition of multiple micronutrient supplement for pregnant and lactating women recommended for trial purposes by UNICEF / UNU / WHO.

Nutrient	Amount
Vitamin A	800 mcg
Vitamin D	200 IU
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B1	1.4 mg
Vitamin B2	1.4 mg
Niacin	18 mg
Vitamin B6	1.9 mg
Vitamin B12	2.6 mg
Folic Acid	400 mcg
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 mcg
Iodine	150 mcg

The meeting was organized in two parts, the first focused on research and the second on policy and programmes. The first four days mainly involved the principal investigators involved in micronutrient supplementation efficacy trials together with representatives from UNICEF, WHO, UNU, HKI and USAID discussing the details of the trials. After having jointly reviewed the various research protocols from the respective trials, the meeting split into two smaller working groups. Whilst one group made up of the principal investigators discussed further the design and ethical issues of efficacy trials and the possibilities for future collaboration, a second group considered the programme implications of the ongoing research. On the final day, the meeting discussed the results of the consultation with a wider audience of policy and programme oriented participants from the World Bank, CIDA, the Wellcome Trust and the Micronutrient Initiative.

Policy context

Policy development for micronutrients has largely been limited to iron, iodine and vitamin A for several decades. If a multiple micronutrient supplement were adopted instead of iron/folate supplements it would be a significant change, and the new product would give a new dimension to programmes aimed at women during pregnancy and lactation. In order to understand the process of moving down the science to policy to programme track, it is instructive to look at how this has worked for these other micronutrients, especially for iron and vitamin A, which are primarily provided as supplements. Understanding what the evidence base was that was used to decide on the adoption of these policies, and how such evidence was accumulated, might help speed the process of adoption of a multiple micronutrient supplement should it be proven efficacious.

The evolution of policy and programmes for improving vitamin A status stretches back over thirty years. The first policy recommendations for vitamin A largely concerned the use of vitamin A supplements for the prevention of blindness[3]. The discovery that the widespread use of capsules not only led to the elimination of blindness but also to the reduction of young child mortality led to the large scale use of vitamin A supplements in different countries to further test for these effects[4]. This process was initially developed through the committee on international nutrition programmes of the Food and Nutrition Board in the US that produced a common protocol for conducting further trials to investigate the effects of vitamin A supplements in the field[5]. As such research gathered pace, a further meeting of this sort was held at WHO in Geneva in 1991, when the principal investigators of ten vitamin A supplementation trials met and agreed how they might collaborate as their respective trials were being conducted[6]. The existence of these common protocols and research designs facilitated the work of the group that carried out the meta-analysis of vitamin A supplementation trials under the umbrella of the ACC/SCN. The report by Beaton et al (1993) found that improving vitamin A status, whether through high or low dose supplements or a fortified condiment, reduced child mortality by 23%[7]. With this came the international recognition that further randomised studies of vitamin A and child mortality with placebo controls would be unethical and that there was now a need to increase investments in vitamin A supplementation programmes. Despite this recognition, by the mid decade there was still no large-scale move to introduce massive dose capsules into programmes. It was only after a technical consensus meeting was held in UNICEF in 1997 and the joint action of both bilateral and multilateral agency consortium called the Vitamin A Global Initiative, that progress was seen in the latter part of the decade[8]. Recent trends for large-scale vitamin A supplementation programmes suggest that more capsules are being distributed and high levels of coverage are being achieved in many countries[9]. One study has reported a change in maternal mortality if preconceptual, periconceptual and postconceptual vitamin A/beta-carotene supplementation is provided[10]. Another is currently underway in Ghana where malaria is common. There is a need to define how much research knowledge is needed before policy can be formulated with regard to vitamin A supplementation of mothers for example. When is enough enough and who decides, be it at the country or international level?

The World Health Organization first formulated a policy that recommended that pregnant women be supplemented with iron supplements in 1968[1]. The primary objective in formulating this policy was to reduce the high prevalence of iron-deficiency anaemia observed in women during lactation and pregnancy across the globe[1]. No thought was given at that time of the need to show or improve beneficial effects of iron supplementation beyond the reduction of anaemia. Since that time however, little more scientific evidence has accrued to support the use of iron supplements for other benefits beyond that of anaemia reduction, and there is a growing concern in some quarters that high haemoglobin levels during pregnancy are not always beneficial[11,12]. The systematic reviews of both iron and folate supplementation conclude that whilst there is evidence that anaemia is improved, there is no evidence of improvement in other birth outcomes such as low birth weight and maternal mortality[13,14]. These systematic reviews have agreed however that there is a lack of studies in resource poor settings amongst women that are likely to be most deficient. In addition to this, there are ethical issues that make it difficult to test the efficacy against a placebo

control since the policy in most countries is to give iron supplements to women during pregnancy. Governments have increasingly adopted this policy as a means to tackle iron-deficiency anaemia and have implemented large-scale supplementation programmes[9]. Yet the prevalence of iron-deficiency still remains high in most countries[15]. This has often been attributed to poor compliance and distribution of supplements, but also the para-professional's lack of knowledge about the supplements[9]. A consensus meeting was held to try to establish the technical consensus to move forward with iron programmes in UNICEF in 1998[16]. But there has not been any large move at the programme level, such that levels of supplements and programmes aimed at trying to reduce iron deficiency anaemia are not moving forward[9]. There is also a growing concern with the risks iron supplementation may bring for some mothers, especially those that don't show haemodilution and the consequent lower hemoglobin levels in the latter part of pregnancy[11,17].

This is the policy environment that forms the backdrop for policy development for multiple micronutrient supplements. The UNU/WHO/UNICEF supplements are similar in formulation to those readily available on the open market in many developing countries, and that are taken by those able to purchase them. The ethical dilemma that surrounds these micronutrient trials concerns the act of withholding them from poor women when it is known that their dietary intakes are below recommended levels for these nutrients. At the same time having evidence that providing the nutrients resulted in measurable improvements in birth outcomes would help convince health economists and senior officials in Ministries of Health that there are strong cost benefits for adopting such supplements. The potential advantage of a multiple micronutrient supplement in pregnancy is simply that iron folate is already being distributed, if it were switched to a multiple micronutrient supplement, then a single supplement could have multiple and important effects on maternal and infant well being. How best to investigate these possible benefits and how to deal with the ethical issues around knowing when to stop the experiment are the issues that need to be dealt with. The group was asked to reflect on these dilemmas and to come up with suggestions during their deliberations.

Programme context

The multiple micronutrient supplements that are being tested in the different country settings are being provided through a variety of different programmatic settings. These interventions are being pursued because the evidence that they are likely to be beneficial is already considerable. In all the UNICEF supported studies, the supplements are being tested as part of a new initiative to prevent low birth weight. At a programmatic level, interventions designed to tackle childhood malnutrition have often had only limited success because of their inability to address the larger problem of low-birth weight[18]. Although a balanced protein energy supplement has been shown to have an effect on low birth weight, few programmes have been proven to prevent low-birth weight, and it is admittedly a difficult outcome to impact upon[19,20,21]. Improvements in birth weight have been shown to be independently associated to maternal weight gain during pregnancy and maternal pre-pregnant weight[19]. The Institute of Medicine in the US introduced recommendations on desirable weight gain during pregnancy that were considerably higher to those recommended prior to 1990[22]. These recommendations have been widely implemented in the US through the Women, Infants and Children (WIC) programmes of the Government, and evidence so far is that these are proving both feasible and beneficial in the US context[23]. However, few programmatic interventions that aim to improve maternal nutritional status and thus pregnancy outcome have been tested in developing country settings. There are no programmatic recommendations from WHO for example, on how to proceed in this area. Increasingly, it is becoming clear that packages of interventions will need to be implemented to improve pregnancy outcome and prevent low-birth weight and that micronutrient interventions should be part of this[19,24,25].

In most programmatic settings, the introduction of the multiple micronutrient supplements will not be a stand-alone activity[26]. It will almost always be part of a package of interventions aimed at improving the health and the nutrition status of the pregnant and lactating mother. To date, interventions that have been implemented to improve maternal nutrition and to prevent low birth weight range from community based food supplementation programmes, such as the BINP programme in Bangladesh, to safe motherhood programmes, be they clinic based as in

the Philippines or community based as in Indonesia. Where malaria is a problem, the use of insecticide treated bed nets is likely to be a programmatic component together with chemoprophylaxis, as is the case in Tanzania where deworming is also part of the antenatal care package. Together, these various interventions provide an opportunity where pregnant women can be given multiple micronutrient supplements; in many cases, the infrastructure is in place, though it may be imperfect. The participants were asked to reflect on these aspects of programme design and context of the multiple micronutrient supplements and make recommendations as to how to best deal with these issues in the extrapolation of the research result to programmes in the future.

Scientific context

Several studies have now shown that poor women in developing country settings consume diets that are micronutrient poor, and in some cases may have diets that inhibit micronutrient absorption (e.g. the high phytate diets based on maize for example). Such diets are more qualitatively than quantitatively deficient, such that even if energy needs are met micronutrient needs are not[27,28]. A recent review by Ramakrishnan et al (1999) on micronutrients and pregnancy outcome found that there was strong evidence from well-designed randomised controlled trials that zinc, calcium and magnesium improve pregnancy outcomes, mainly affecting pre-maturity, birth weight, and pregnancy-induced hypertension[29]. The authors found the effect of other single micronutrients on pregnancy outcome to be inconclusive, mainly due to weak study designs and small sample sizes. They recommended that further research be undertaken particularly for iodine, iron, folic acid, and for multiple micronutrient supplements, specifically in relation to pregnancy outcomes (e.g., birth weight and perinatal mortality). Recent research on vitamin A and pregnancy outcome by West et al (1999) found that supplementing women of reproductive age with a weekly low dose of vitamin A in Nepal significantly reduced maternal mortality in those mothers that became pregnant by 44%[10]. Importantly, recent research in Tanzania shows that multiple micronutrient supplements significantly improved pregnancy outcome in HIV-positive women, reducing LBW by 44%, pre-term delivery (<34 weeks) by 39%, and IUGR by 43%[30]. In view of the considerable variations in infection load between communities (e.g. malaria and HIV), there needs to be clarification on what 'scenarios' need to be defined for vitamin A studies to be performed. Defining how to assess micronutrient status in pregnancy and lactation in the presence of infection, especially becomes an important research issue.

All of these findings indicate that it is reasonable and useful to further test a multiple micronutrient supplement to determine the size of the effect on pregnancy outcomes. The research trials to test micronutrient supplements that are planned or currently on-going provide an opportunity to maximise on these research findings. A meta-analysis of these studies would allow a more consolidated analysis of their findings and help create the cast iron scientific arguments needed to convince Ministries of Health to invest in such interventions should that prove warranted. Although there is concern that when combined, some of the micronutrients may interact with one another and thus inhibit absorption, there is some evidence suggesting that absorption of certain nutrients such as iron may actually be enhanced[27]. Every effort should also be given to ensure that such trials have the capacity to detect any adverse consequences at an early stage, even though this may be considered to be very remotely possible. The group was asked to reflect on these issues during their deliberations and to make recommendations on how to deal with them.

Description of studies

The principal investigators from eight planned or on-going efficacy trials of nutrient supplementation during pregnancy were invited to attend this meeting. The studies included for joint examination are either planned, underway or completed, in Pakistan, Bangladesh (two studies), Nepal (two studies), Guinea-Bissau, Indonesia, Tanzania, and Niger. All are randomised controlled trials, and with the exception of the Johns Hopkins' Bangladesh study, all are multiple micronutrient supplementation efficacy trials. Each one intends to supplement pregnant women with a multiple micronutrient supplement. The supplements used in the different trials are largely similar. With the exception of the Johns Hopkins' Bangladesh study

and the Harvard Tanzania study and the Johns Hopkins' Nepal study, all others will be or are using supplements based on the UNICEF/WHO/UNU formulation, as described in Table 1. These studies vary in design and duration of supplementation, but the outcome variables measured in each of the studies are similar for most studies. The study design details are given in Annex 1.

The Aga Kahn study in Pakistan aims to determine which of four interventions during pregnancy will improve maternal nutritional status and infant birth weight, and reduces the prevalence of low birth weight in the sample. It is designed as a cluster randomised control trial with a 2x2 factorial design. Thirty clusters will be divided into four cells with a total sample size of 1600 pregnant women. Each cell will be randomly allocated to receive one of four interventions including either a multiple micronutrient supplement or an iron-folate supplement with or without nutrition education. The main outcomes measured will be birth weight and maternal nutritional status

In Nepal, the primary aim of the CICH study is to evaluate the effect of antenatal multiple micronutrient supplements on birth weight, gestation, and perinatal infections in mothers and infants. This is a double-blind randomised control trial where 1200 pregnant women will be randomised at the individual level to receive either an iron-folate supplement or a multiple micronutrient supplement. The main outcomes being measured will include birth weight, perinatal mortality, maternal nutritional status, and maternal immunological status (on a sub-sample).

The Royal Veterinary and Agricultural University study in Guinea-Bissau aims to determine the effects of antenatal multiple micronutrient supplements on pregnancy outcome, and peri- and neonatal mortality. It is designed as a double blind randomised controlled intervention study where 2250 pregnant women will be randomised at the individual level to receive one of three treatments. One arm will receive iron-folate supplements, the second will receive a multiple micronutrient supplement equivalent to one RDA, and the third arm will receive twice the RDA. The main outcomes measured will be maternal nutritional status, birth weight, peri- and neonatal mortality, infant mortality, and early infant growth.

The primary research aim for the Johns Hopkins' study in Bangladesh is to determine whether supplementing women of reproductive age with a single RDA of vitamin A can reduce all-cause pregnancy related mortality by 35% or more. The study is designed as a cluster randomised double blind placebo controlled trial. Women of reproductive age will receive a weekly supplement of a placebo, a vitamin A capsule of 7000 retinol equivalents. The planned sample size is 54000 pregnancies. The main study outcomes are maternal mortality, foetal loss, and infant mortality.

The HKI study in Indonesia aims to assess the relative impact of multiple micronutrient supplements compared to iron/folate supplements on maternal mortality, infant mortality and low-birth weight. This is a community-based cluster randomised double blind intervention trial. Pregnant women will be supplemented with either the multiple micronutrient supplement or an iron-folate supplement. The intended sample size is 126000 pregnancies. The main study outcomes are maternal mortality, infant mortality, low birth weight, and maternal biochemistry.

The study aims of the ICDDR,B study in Matlab, Bangladesh are to determine whether supplementing pregnant women with a multiple micronutrient supplement will significantly improve maternal haematological status or birth weight. It will also look at the interaction between supplements and early or late food supplementation. This is a double blind randomised controlled study where pregnant women will be randomised at the individual level. It follows a 2x3 factorial design (6 cells) and intends to recruit 3000 pregnant women. Three cells will be started on food supplementation early in pregnancy and the remaining three will begin food supplementation later in pregnancy. A third of the women will receive a multiple micronutrient supplement, a second group will receive a low-dose iron-folate supplement, and the third group will receive a high dose iron-folate supplement. The main outcomes measured will include birth weight, maternal haematological status, pre-term delivery, weight gain during pregnancy, gestational age, and maternal micronutrient status.

The primary research aim for the Harvard study in Tanzania is to determine whether supplementing HIV negative pregnant women with a daily multiple micronutrient supplement will reduce the risk of foetal loss, low-birth weight, and pre-term delivery

compared to women who receive an iron-folate supplement. The study is a clinic-to-community double blind randomised controlled intervention study where women will be randomised at the individual level. Pregnant women will be randomly allocated to receive either a multiple micronutrient supplement or an iron-folate supplement. The micronutrient supplement has several nutrients in multiple RDA doses, and as such is more a pharmacological than physiological level of supplementation. The intended sample size is 6000 HIV negative pregnant women. The main outcomes measured will include foetal loss, low birth weight, and pre-term birth.

After having discussed all these protocols it was decided to focus further discussions only on the five studies that will be using the UNICEF/UNU/WHO supplement. The Tanzania study will be supplementing women with a multiple micronutrient supplement containing pharmacological doses of micronutrients, which differs from the aforesaid formulation. The Johns Hopkins' Bangladesh study is looking at the effects of vitamin A, and has no multiple micronutrient supplements included as yet, and the finished study of Johns Hopkins in Nepal did not use the UNICEF/WHO/UNU supplement formulation. The study design for the HKI study in Niger is still being formulated, and was therefore not discussed. The group felt that of these eight studies, only five should be discussed more thoroughly. Because of these fundamental differences, it was felt that any eventual pooled analysis would only include these five studies. It was made clear though that other trials not discussed at this meeting could be included in an eventual pooled analysis as long as the trials were consistent with the basic guidelines and recommendations defined at this meeting.

Discussion of outcome measures

The unifying feature among all the studies is that they intend to measure birth weight as the dependent outcome variable. They also assess maternal nutritional status, mainly maternal weight and height. Some of these studies will also undertake more thorough assessments of biochemical status. Four studies will assess infant growth in the first year of life. The Indonesian study will look at maternal mortality. Details about the outcome measures for each study are given in Table 2.

Several issues were discussed with regard to the outcomes measured in these studies. The discussion centred on three major issues namely obtaining accurate birth weights, measuring the stillbirth/neonatal mortality rate and head circumference. It was agreed that every effort should be made to get birth weight within 24 hours of birth. A locally constructed normogramme could be used to validate the use of weights taken beyond 24 hours. The disadvantage of using such a normogramme is that it artificially restricts the variability attributed to those birth weights. Although the UNISCALE only weighs to the nearest 100g it is still an accurate scale. In reality weighing to less than 100g gives a false idea of accuracy since weighing procedures cannot ensure that the baby is weighed with an empty stomach and an empty bladder, and these two alone can produce differences in weight of 100g or more. The effect of only weighing to 100g as compared to using a balance that weighs to the nearest 10g does not seem to affect the variance of the measure, but this merits further investigation. The sample size calculations for birth weight are all calculated based on estimates of variance associated with the use of "normal" balances that weigh to 100g and not the more precise scales that weigh to 10g. Whilst 10g precision was called for in metabolic work with new born babies, for population based studies such precision is of dubious value. The UNISCALE is being used to construct the new growth curve being prepared by WHO, and the investigator group from that study has checked the precision and accuracy of the scale for this purpose. The various documents available on precision, accuracy and ease of use of the UNISCALE should be shared with the principal investigators. All trials should routinely check for precision and accuracy of scales on a three monthly basis.

It was felt that the use of birth weight alone to measure the efficacy of multiple micronutrient supplements is not advised. The spectrum of abortion, miscarriage, stillbirth, and neonatal mortality is an important one to investigate. Most studies will also measure perinatal mortality. Those that do not are seeking extra funds to be able to include these outcomes. The investigation of these events requires the construction of verbal autopsy methods. Standardized tools exist that can be

adapted to the local cultural context. Pakistan and Indonesia have already developed tools which cover these aspects and have agreed to share it with others as appropriate.

It was suggested that measuring head circumference would be important for advocacy purposes to help allay the myth that bigger birth weight will mean more difficult births. All trials agreed that they would measure head circumference. Researchers felt that to measure haemoglobin, venous blood is preferred over capillary blood. However, assessing haemoglobin by using a haemocue was thought to be acceptable as long as care is taken with the use of haemocue cuvettes. It was felt that these trials should include instruments to investigate maternal night blindness and treatment protocols for women with night blindness in their sample. Several trials are attempting to capture maternal morbidity. Some are using a periodic recall. Others recognizing the difficulty of getting reliable data from recall methods are using biochemical markers of infection. The desirability of developing local data safety and monitoring boards to manage the ongoing ethical aspects of such trials was agreed by all. Indonesia is most advanced in this and others would like to learn from them.

Table 2: Outcomes being measured in the five studies

Outcome	Pakistan	Nepal	Guinea Bissau	Bangladesh	Indonesia
Birth weight	Yes	Yes	Yes	Yes	Yes
Head circumference	Yes	Yes	Yes	Yes	Yes
Infant development	Yes	No	No	Yes	No
Infant growth	Yes	No	Yes	Yes	Yes
Infant morbidity	Yes	Yes (neonatal)	Yes	Yes	Yes
Perinatal and neonatal mortality	Yes	No	Yes	Yes	Yes
Gestational age	Yes	Yes	Yes	Yes	Yes
Maternal night blindness	Yes	No	No	Yes	Yes
Maternal anaemia	Yes	Yes	Yes	Yes	Yes
Maternal micronutrient status	Yes (iron, zinc, retinol, and carotene)	Yes (retinol, Vit C, Vit E, carotenoids)	Yes (folate, retinol, Vit E, iron, carotene)	Yes (iron, retinol, carotenoids, tocopherol, selenium, arsenic)	Yes (B-vitamins, retinol, carotenoids, Vit E, Fe, Zn, Cu, Se)
Maternal anthropometrics	Yes (weight gain)	Yes (height, weight)	Yes (height, weight, MUAC)	Yes (weight gain, weight, height, skin folds, MUAC)	
Maternal morbidity	No	Yes (lab)	No	Yes	Yes
Maternal mortality	No	No	No	No	Yes

The outcomes denoted in **bold** are the dependent variables in the hypothesis being tested and for which sample size calculations were developed. The other outcomes are being measured for use in the analysis as independent variables, and may be effect modifiers. Some of these outcomes may also show a treatment effect. They may also be used to check for confounding variables.

Discussion of main interventions

Broadly, four important issues were discussed with regard to the interventions being implemented in each trial. These were to ensure and enhance compliance, to increase internal and external validity, and the formulation of the supplement. The suggestions as discussed by the group are given below. Details of the planned interventions for each study are given in Annex 1. Table 3 presents a summary of the sample size and power calculations, the planned analysis, and details of the ethical approval obtained for each study.

Adherence

The investigators recognized that the effort put into trying to verify the degree of adherence with the experimental protocol with regard to taking the supplements was critical. The difference between efficacy and efficiency trials largely revolve around whether the treatment is provided by a third party or self-administered. In large scale trials carried out through regular programme infra-structures (as is the case in the five studies concerned) it is vital to prove that treatments are taken.

The investigators felt that checking adherence (commonly called compliance) by pill counting should be done more frequently than just monthly. The validity of pill counting could be improved by providing more supplements than needed that could then be replenished periodically (e.g. provide 45 pills and the fieldworker would return in 28 days to replenish). A suggestion was made to assess urinary riboflavin or erythrocyte riboflavin randomly, which would be useful to give an indication of compliance at the group level, but not at the individual level. Indonesia has a predictive index of compliance that is used to identify mothers requiring special attention; it was felt that this could be shared with others. Recommendations about how the supplements were to be taken whether on an empty stomach or after meals need to be clear as they would differ by context due to variations in traditional diets (e.g. high phytate diets that could inhibit absorption).

Enhancing adherence

The investigators agreed that as is amply shown in the literature, one of the most important determinants of adherence is the subject's belief in the good intentions of the health provider. All felt it is important to adequately train staff so they understood how to counsel participants on potential side effects and to enquire about and document these side effects. It is important to ensure that subjects understand what to expect and what not to expect from the supplement (i.e. it is not a headache pill or an antibiotic). To enhance adherence, Indonesia and Pakistan have also undertaken/plan to undertake community and social marketing activities.

Internal and external validity

Suggestions to increase internal and external validity were to take a random sample of supplements from the field at various time-points in the study and to test them locally and send them to an independent lab for testing. Tests can include testing for degradation of folic acid, vitamin E and/or vitamin A. Most sites don't have the funds or resources for this and would require external help to make it happen.

Formulation of supplement

Multiple doses of RDAs may be necessary in populations where disease states are excessively high (e.g. malaria/ HIV) or where dietary inhibitors are present in high amounts. Trials may use formulations other than the UNICEF/UNU/WHO supplement but, if so, should compare these variant supplements with the basic supplement. The issue of whether the supplements are halal or non-halal was largely resolved. Indonesia has dealt with this by using a capsule with fish oil encapsulation. It was also noted that a letter had been shared at a WHO/UNICEF meeting in the Middle Eastern Region, which had been produced by prominent members of several Islamic states stating that the gelatin used to coat tablets has been processed so much that the product used is considered acceptable in Islamic communities.

Table 3 Planned interventions

Site	Interventions	Methods to check adherence	Enhancing adherance	Supplement Type	Duration of Supplement-ation	Standard-ization	Tech-niques Internal validity	External Validity
1. Pakistan	1. MMC 2. MMC and nutrition education 3. Iron-folate 4. Iron-folate and nutrition ed	• Pills to be taken daily once • Pill counting and replacement • Checked every 2 weeks	• Maternal usage and acceptability of supplement and energy protein supplement • Community education	Enrolment at 16-20 weeks to delivery and 3 months post-partum	Tablet – UNICEF MMN Iron/Folate 60/400	Standard UNICEF/WHO recommended supplements and antenatal care	(within study testing of tabs)	(tabs sent out for testing)
2. Nepal	1. MMC 2. Iron-folate	• Monthly in-clinic pill counting • Fortnightly pill counting • Monthly home visit pill counting • Self-admin-istered sup-plements taken daily once • Change in maternal blood mi-cronutrient status	• Fortnightly counselling	From a maximum of Week 20 to delivery	UNICEF MMN Tablets and Iron/Folate 60/400	Standard UNICEF/WHO recommended supplements		6 monthly analysis of tablet constitue nts by third party lab-oratory
3. Guinea-Bissau	1. MMC (1 RDA)* 2. MMC (2 RDA) 3. Iron and folate *1 will be the UNICEF tablet produced by the UNICEF supplier	• Supplements distributed every 2 weeks until delivery • Taken once daily • Pill count and replenish every two weeks	• Women will be instructed on the importance of regular intake of the tablets for her and her baby's health	Week 16-35 to delivery	UNICEF MM Tablets (1 RDA, 30mg Iron), MM Tablets (2 RDA, 30mg iron) or iron/folate Tablets (60/0.4mg) Women with severe anaemia were given an additional iron/folate Tablets All three tablets are identical	Standard UNICEF/WHO recommended supplements		

Table 3 Planned interventions (continued)

Site	Interventions	Methods to check adherence	Enhancing adherance	Supplement Type	Duration of Supplement-ation	Standard-ization	Tech-niques Internal validity	External Validity
4. Bangladesh – 2	Individual-level randomised intervention trial I) Early calorie supplement ation 1. MMC 2. Iron-folate 30/400 3. Iron-folate 60/400 II) Usual supplement ation 1. MMC 2. Iron-folate 30/400 3. Iron-folate 60/400	Pills to be taken daily once Pills to be replenished monthly. Special electronic equipment called eDEM, will be used to monitor adherence. This method will be compared with other measures of compliance such as pill-counts and recalls of the pregnant women.		Micronutrient supplementati on from week 14 to 3 months post partum.	UNICEF MMN tablet Iron-folate tablet (30/400) Iron-folate tablet (60/400) All tablets look alike	Standard UNICEF/WHO recommended supplements and antenatal care		Tablets sent out for testing
5. Indonesia	1. MMC 2. Iron-folate	• Pills to be taken daily once • Supplements will be distributed monthly • Field workers will check adherence by spot-checking and pill-counting • Biochemical indices will be assessed to check for erythrocyte enzymatic activity for riboflavin, plasma vitamin A and zinc • Adherence will be checked 3x a month • Fieldworkers will check if anyone else is taking the capsule • Use the predictive index of compliance • Random inspections	Qualitative assessment of perceptions and attitudes towards prenatal supplements Social marketing	Enrolment to delivery (enrolled as soon as identified as pregnant)	UNICEF MMN formulation in locally produce capsule Iron-folate 30/400		Check capsules in Indonesia	Check tabs in Copenha gen

Group discussion of the scientific and study implementation issues

The group of principal investigators discussed a series of issues related to common indicators and variables, biomarkers, ethics, analysis, and further need for increased coordination. The various common variables that all studies should collect to help typify the study population and to demonstrate that randomisation worked include: rural/peri-urban/urban settings; SES indicators, including ownership of house and other assets, and environmental sanitation; education; health system indicators including home births, birth attended by trained attendants, anti-malarial and bed net use in malarial areas; age; parity; previous pregnancy outcome; gestational age at enrolment; date and season of enrolment; maternal nutritional status (weight, height, MUAC); substance use including tobacco, alcohol and betel nut; birth weights taken within 24hrs, 24-48 hours, 48-72 hours.

The biomarkers recommended for use in such studies were of two types: the core biomarker indicators are that all studies should include haemoglobin, ferritin and serum retinol. Additional indicators to be considered for inclusion included serum zinc, transferrin receptor, serum and red cell folate, urinary and red cell riboflavin, vitamin C, and total carotenoids. The acute phase reactant proteins (ACT, AGP, and CRP) are also recommended as markers for infections.

On ethical issues the group agreed that whilst ethics' committees in both sponsoring institutions and funding agencies had cleared most studies as a standard requirement, in few places was a local capacity created to monitor the trial as it progressed. The use of local data safety and monitoring boards was strongly recommended in all studies. The group with the best experience in this was the HKI study in Indonesia. The possibility of linking up core members of data monitoring boards in each site in order to transfer capacity is one possibility for future action, but this would require extra funds.

Any future analysis, be it joint or individual, should be developed with an "intent to treat" approach and follow the CONSORT guidelines (www.consort-statement.org) for the consolidated standards of reporting randomised control trials. These analyses should consider potential confounders and effect modifiers as discussed below and look at birth weight, gestational age, and mortality (as rates and relative risks) and survival outcomes.

A discussion about the possible confounders or effect-modifiers led the group to develop a list of which variables it would be advisable to collect.

Table 4. List of required and recommended confounders and effect-modifiers to be recorded.

Parameter*	Required	Recommended
Maternal height at enrolment	X	
Maternal weight at enrolment	X	
Parity	X	
Age at enrolment	X	
Previous pregnancy outcomes	X	
Smoking habits	X	
Alcohol/substance abuse	X	
Date of last menstrual period	X	
Other supplements consumed	X	
Date of enrolment (seasonal issues)	X	
Date of delivery X Time of birth	X	
Time of weighing infant	X	
Completed years of education	X	
Who was present at delivery	X	
Bednet use and anti-malarial use	X	
Maternal work load		X
Maternal MUAC		X
Number of antenatal care visits		X
Dietary habits		X
Domestic violence		X
Water and sanitation		X
Night blindness during pregnancy		X
Exposure to domestic smoke		X

* order not indicative of importance

Table 4 presents which data would be required and which would be recommended. This is the key information that would need to be collected to describe the study population and facilitate comparability between studies and enable analyses including other factors likely to influence outcomes such as birth weight, infant mortality, and maternal mortality

The group agreed that some form of continued liaison after the meeting was very desirable for continued information sharing, technical updates and troubleshooting. The notion was put forward of creating a mailing list for a Multiple Micronutrient Interest Group that should include all key players, especially those from developing countries. The group supported the idea that such a capacity be created at CICH. Another meeting of the group was requested within the year and that should be held in South Asia, and include the expanded group of constituents. It was agreed that such a meeting should attempt to bring additional expertise on board including: basic scientists, reproductive health experts, randomised control trial experts and biostatisticians, and public health experts.

Group discussion of the process of policy change and programmatic implications

The discussions by the non-investigator group on the process of policy change and how the provision of multiple micronutrient supplements could be achieved at a programmatic level focused on several areas. Firstly, the group recognised that policy implementation would need to occur at several levels, at the international, national and/or district levels. At each level, the benefits of the intervention based on consistent and plausible research findings would need to be clearly presented and defined. International agencies and consultative groups and national governments would have to be convinced of the benefits and that implementation would be affordable, especially within strategic partnerships. To be convinced of the need for policy change, policy-makers would need to see changes/improvements in key indicators. The group felt that the indicators of greatest interest included monitoring the prevalence of low birth weight; maternal mortality and morbidity; infant and young child mortality and morbidity; maternal nutrition; breast milk nutrition; anaemia; vitamin A deficiency; and child development. The group also felt that the infrastructure by which supplements could be made available was already in place. Enabling activities that could support multiple micronutrient supplementation included malaria, HIV, de-worming and STD control programmes; pelvic infection treatment programmes; birth spacing activities; safer motherhood initiatives; and integrated management of childhood infection programmes. All of these programmes provide an opportunity for supplementation and a point of contact.

Sectors through which multiple micronutrient supplementation could be undertaken included health systems, such as antenatal care and immunization programmes; community health programmes, such as national immunisation/HIV days; social development programmes, such as community groups/NGOs. But it was clear that for inclusion of a multiple micronutrient intervention there was a need to identify the full cost of activities and the added value of multiple micronutrient supplementation to specific sectoral activities. The key question is what is the added value of micronutrients over and above the various other components of an integrated package of interventions aimed at improving birth outcomes. For these reasons the planned trials should all attempt to develop cost benefit analyses.

Efficacy trials could shed light on other policy and programme issues. The group felt that facilitating factors might need to be included in “routine” programmes, such as sharing methods of monitoring compliance. Efficacy trials could provide the necessary information for IEC programmes, and could guide cost/benefit analyses. These trials would also provide a clearer definition of what could be claimed for a multiple micronutrient intervention, and provide information of unexpected findings and adverse effects.

Assuming that efficacy of the multiple micronutrient supplements is shown, then effectiveness studies that enable the comparison/validation of the multiple micronutrient intervention when applied in different contexts would eventually be needed. The idea that

such effectiveness trials be run in parallel with the efficacy trials could permit greatly cutting the time for translation of science into programmes. It was agreed that effectiveness studies could be "risky" if applied within dysfunctional health/community programmes. On the other hand such studies should seek to identify levels of adequacy and plausibility concerning the delivery of the programme interventions, in order to be able to understand what works and what doesn't work. Such "operational" research that could identify where the "blocks" are when and if a multiple micronutrient intervention were introduced could be useful. The group felt there would be a need to examine the supply and demand aspects of a multiple micronutrient intervention and to examine the additional cost of achieving whatever "added value" these supplements might bring.

Conclusions and recommendations

On the final day, the findings and recommendations of the smaller group were presented to an expanded group of participants, which included representatives of Canadian CIDA, The Wellcome Trust Foundation, The World Bank, The Division of Reproductive Health of WHO, USAID, Helen Keller International and the Micronutrient Initiative. After discussion with this expanded group, it was largely agreed that the various organizations present could and should help support and carry forward the recommendations of the meeting.

The meeting was considered to have been successful at discussing design issues in that the researchers agreed upon which outcomes would be important to measure, how compliance could be ensured and enhanced, how internal and external validity could be increased, and which confounders or effect-modifiers would need to be included in data collection. Participants were open to the idea of increased comparability between studies and the possibility of an eventual pooled analysis. The minimum criteria for study design for other trials to be included were agreed upon and basic guidelines were developed. Collaboration across sites in the sharing of experience in developing standardized tools, such as verbal autopsy (abortion/miscarriage, stillbirth/neonatal death), and night blindness was initiated. All agreed the desirability of developing local data safety and monitoring boards to manage the ongoing ethical aspects of such trials. Indonesia is most advanced in this and others would like to learn from them. Pathways to facilitate the process of policy change and enabling activities that could support the eventual distribution of multiple micronutrient supplements within safe motherhood initiatives were also discussed, including the need for effectiveness trials to be run in parallel with the efficacy trials.

The participants felt strongly that this meeting was very constructive and useful and had provided them with an opportunity to share ideas. It was felt that further on-going collaboration across study sites would be desirable for information sharing, updates, and troubleshooting. An expanded electronic mailing list was suggested for all constituents working on multiple micronutrient supplementation trials, for both efficacy and effectiveness studies, especially from developing countries. A further meeting was called for, which preferably should meet in South Asia within a year, involve an expanded set of constituents and bring extra expertise onboard. A suggestion was made that a literature review of the effects of micronutrients in the UNICEF/WHO/UNU multiple micronutrient supplement would be useful for programme managers.

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High rates of maternal morbidity and mortality are all too often the tragic outcome of pregnancy in poor countries. Many factors contribute to these, among them is nutritional deficiency of a number of micronutrients. As a result of a WHO/UNICEF collaboration a new product – a multiple micronutrient tablet – has been developed which provides important micronutrient supplementation on a daily basis during pregnancy and early lactation. The impact of this new preparation is being assessed in a number of countries and this review summarises the design and data analysis issues of the various efficacy trials.

A meeting held at the Institute of Child Health in March 2002 provided a unique opportunity for investigators to collaborate in study design and data analysis. It also provided an excellent opportunity to place the results within a policy and programme framework at an early stage.

The meeting was generously supported by the Micronutrient Initiative who play a key role in promoting nutritional health of women and children through improving micronutrient status in poor countries.

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