

JHU-JiVitA Technical Report to MI-DICA, January 2004

JiVitA Bangladesh



**Maternal and Infant Micronutrient
Research Program in Bangladesh
Centre/MI File: 5600-0007-02-300**

**Technical Report and
Proposed Activity Plan and Budget**

submitted to

**The Micronutrient Initiative/
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Executive Summary

“Jibitau”¹ in the Bengali language means “alive”; thus, “JiVitA Bangladesh” is translated to mean “Alive Bangladesh”, a collaborative research project dedicated to determining the efficacy of micronutrient and other practical nutritional approaches to improving the health and survival of mothers, infants and children in rural Bangladesh and, more broadly, in the South Asian Region.

JiVitA is a joint undertaking by the Center for Human Nutrition, Department of International Health of the Johns Hopkins University Bloomberg School of Public Health, Baltimore MD, USA (JHU) and the Ministry of Health and Family Welfare (MOHFW) of the Government of Bangladesh (GOB) under the National Integrated Health and Population Program (NIPHP) of the MOHFW, GOB and the US Agency for International Development (USAID), Dhaka. Established in January 1998, and now operating in a rural population of ~580,000 in the Districts of Gaibandha and Rangpur in northwestern Bangladesh, the Project seeks to improve maternal and child health by evaluating the efficacy and safety of micronutrient and other nutrition interventions through the conduct of intervention trials and epidemiological studies, training, providing technical assistance and offering policy guidance related to nutrition interventions nationally and within the region. JiVitA enjoys collaboration in its research and training activities with several national, regional and international centers, including the Institute of Nutrition, University of Dhaka; the National Institute for Preventive and Social Medicine (NIPSOM), Dhaka; the International Atomic Energy Agency (IAEA) through the Bangladesh Atomic Energy Commission (BAEC) in Dhaka, Bogra and Rangpur; the Rangpur Medical Center (RMC), Rangpur; the Institute for Child and Maternal Health (ICMH), Dhaka; and the Institute of Nutrition at Mahidol University (INMU), Salaya Campus, Thailand.

JiVitA further shares a unique relationship with another large, population-based nutrition and health research activity in the region, its sister public health research project - the Nepal Nutrition Intervention Project-Sarlahi (NNIPS), with a trained staff of ~550 working in a population of nearly 300,000 people – which has a long history of child and maternal micronutrient and health intervention research under the scientific direction and coordination of the same research team at JHU. Together, NNIPS and JiVitA have completed or are presently carrying out seven micronutrient intervention trials that have enrolled, supplemented and followed over 130,000 infants and preschool children and nearly 120,000 women of reproductive age, with more than 60 scientific publications to date having emerged from NNIPS alone addressing effects of vitamin A, beta-carotene, folic acid, iron, zinc and other micronutrients on child and maternal survival, health and function (eg, see refs 1-30). The ability to

¹ Pronounced “Ji-vee’-tau”

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communicate and coordinate visions, goals, plans, protocols, procedures, administrative policies and other activities between JiVitA and NNIPS enables these two research projects, working in a combined rural South Asian population of nearly 1 million, to “feed off one another” and accelerate research on key nutrition and health priorities and provide stronger policy evidence for interventions in South Asia.

Establishing the JiVitA Bangladesh research project and setting of its initial goals has been motivated by findings from several NNIPS trials in recent years that revealed the potential for maternal dietary supplementation with (1) vitamin A or beta-carotene to markedly reduce risk of mortality related to pregnancy (16), (2) folic acid and iron to reduce risk of low birth weight and infant mortality but with (3) a multiple micronutrient combination to improve birth weight without commensurate effects on infant survival (25,29). JiVitA has also drawn direction from two other JHU sister projects, in Indonesia in the mid-nineties (31) and, more recently from Tamil Nadu in southern India (32), that have shown supplementation with vitamin A *at birth* to markedly reduce risk of infant mortality. The findings of these trials have stimulated enormous interest to affirm and extend knowledge of these effects, and to provide the required evidence for developing the most beneficial, safe and appropriate combinations of micronutrients for routine maternal, infant and child use in the South Asian region. Thus, the JiVitA Project has, at present, three major research aims to address in a previously not-studied, large, rural population in Bangladesh:

Estimate the impact of maternal, low-dose vitamin A or beta-carotene supplementation on mortality related to pregnancy (JiVitA-1);

Estimate the impact of administering a single large dose of vitamin A to newborns on infant mortality (JiVitA-2);

Test effects of alternative combinations of supplemental antenatal micronutrients on intrauterine growth, preterm delivery, fetal loss and infant mortality (JiVitA-3).

Briefly, JiVitA-1 began in August 2001. Its intended sample size is 68,000 pregnant women. Enrollment is planned to be complete by November 2005 and all fieldwork finished by December 2006. JiVitA-2 is being launched in January 2004 with an intended sample size of 26,000 live born infants. Enrollment is planned to finish by March and field work completed by December 2006. JiVitA-3 is currently being planned to start by December 2005 with a planned sample size of 36,000 pregnant women. Enrollment is expected to be completed by December 2007 and field work by December 2008.

With in-country negotiations starting in January 1998, and following 3 ½ years of development, the JiVitA Project launched its first, currently ongoing JiVitA-1 maternal vitamin A and beta-carotene supplementation trial in August 2001. Presently, the Project maintains a 5-weekly, home-based, hcg urine test

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pregnancy surveillance system among ~110,000 married women living in 596 communities (sectors); all communities have been mapped and 130,000 households addressed and registered in a project GIS system; JiVitA-1 enrolls, supplements and follows ~15,000 pregnancies each year. In a substudy area, each year the project carries out enhanced assessment protocols on ~600 mothers and their infants, including gestational and post-partum phlebotomy, clinical examinations, body composition assessment, diagnostic tests for STDs, proteinuria and diabetes, dietary and behavioral evaluations, measurement of birth size and infant growth rates, among other assessments in order to enrich impact data on potential mechanisms of supplement action and to reveal risks and qualities of life within this typical, rural Bangladeshi study population. The data entry center in Rangpur processes and enters onto the computerized database about 25,000 records each month. To perform this work, as of January 2004, the JiVitA Project employs approximately 770 staff, including ~680 local women who have been hired and trained into field distributor, interviewer, supervisory, quality control, data management and administrative positions. The Project is served by a full-time Bangla research team of 10 physicians, nutritionists, epidemiologists and social scientists and a full-time JHU team of 9 investigators and technical staff, 3 of who are resident in Bangladesh. The Project has two national advisors and a national technical committee 12 prominent health scientists organized under the Secretary for Health within the MOHFW. Each year Project activities are reviewed and approved under the GOB-USAID National Integrated Population and Health Program.

JiVitA is primarily funded by the Office of Health, Infectious Diseases and Nutrition and the Bangladesh Mission of the US Agency for International Development (USAID), Washington DC and Dhaka, most recently as part of a new "Global Research Activity" (GRA) grant to the Department of International Health at JHU, and by the Bill and Melinda Gates Foundation, Seattle, WA. Additional funding is gratefully acknowledged from the Micronutrient Initiative, Ottawa, Canada that has been provided, to date, specifically for the purchase and support activities related to distribution of micronutrient supplements within the JiVitA Project. Additional limited resources have been received from the Sight and Life Research Institute, Baltimore, MD, and the Nutrilite Division of the Access Business Group LLC, Buena Park, CA, USA.

Progress Report for JiVitA-1: Maternal Vitamin A or Beta-Carotene Supplementation Trial to Reduce Maternal Mortality

Background

Maternal mortality represents a major public health problem in the developing world, especially in South Asia where risk of maternal death is roughly 60 times that observed in North America. In Bangladesh, ~20,000 women die each year from causes related to pregnancy (33). A recent Government target has been to reduce the maternal mortality ratio from its present national average of 440 to 300 per 100,000 births (33) through improved antenatal and obstetric care. Both these rates and goals are similar for other countries within the Southern Asian region. While advances in antenatal and essential obstetric care will undoubtedly contribute to reducing maternal mortality (34,35), research is urgently needed to identify other preventable causes of maternal, fetal and infant mortality, especially related to nutritional deficiencies.

Adequate micronutrient intakes among women may play critical roles in insuring reproductive health and survival of mother, fetus and infant in undernourished populations. Seven decades ago, a time period when maternal mortality was on par with developing countries today, a trial in London showed that daily vitamin A supplementation, at recommended levels, could markedly lower the incidence of puerperal sepsis (36), one of several major causes of maternal death. Similar findings were recently reported from Indonesia where the incidence of puerperal fever was lowered in women receiving low-dose vitamin A (37). Recently, the JHU NNIPS-2 trial in Nepal observed a 44% reduction in all-cause mortality related to pregnancy among women who were supplemented weekly with normal dietary amounts of vitamin A, either preformed (7,000 µg retinol equivalent [RE] or 23,000 IU) or as β-carotene (16). These results were seen in a population in which 10-20% of pregnant women normally develop night blindness during pregnancy (6,11), similar to rates observed among pregnant women in Bangladesh (33). Investigation into causes of maternal deaths indicated decreases in infectious and obstetric causes of death by 22% and 27%, respectively, among women taking either vitamin A or beta-carotene, although these reductions were not statistically significant (16).

The findings from Nepal with respect to potential effects of achieving normal, maternal dietary intakes vitamin A and beta-carotene generated considerable interest about micronutrient supplementation to improve maternal health and survival in undernourished and underserved settings, providing the impetus to launch the JiVitA Bangladesh research program.

Primary Aims

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The primary aim of JiVitA-1 is to determine whether weekly maternal supplementation with either vitamin A or beta-carotene, starting early in pregnancy through the first three months postpartum, at recommended levels, reduces mortality related to pregnancy by at least 35%, accepting probabilities of Type I and II errors of 0.05 and 0.20, respectively, with appropriate adjustment for design effect. Although the aim to detect a 35% or greater reduction in mortality for each of the two supplement groups in comparison to control has motivated sample size estimation, it is the intention to compare both supplement groups combined against the placebo outcome as well.

Second, the JiVitA-1 will establish the impact of maternal vitamin A or beta-carotene use on risk of

- miscarriage,
- still birth and
- infant mortality.

Third, the trial will examine impact of maternal vitamin A or beta-carotene supplementation on the following secondary outcomes:

- Maternal morbidity due to infections and other causes;
- Obstetric complications;
- Gestational age at birth, including incidence of preterm delivery;
- Intrauterine growth;
- Infant growth through three months of age;
- Infant morbidity during the first three to six months of life;
- Maternal and infant status with respect to vitamin A and beta-carotene, other carotenoids, tocopherols and other measures of antioxidant status;
- Maternal anemia; and
- Maternal anthropometric status and body composition.

Secondary Aims

In addition to supplementation impact goals, as a large population-based, concurrent, prospective study being carried out in a typical, densely populated and underserved rural area of Bangladesh, JiVitA-1 and its various substudies is capable of addressing numerous epidemiological issues in maternal and infant health and nutrition that are relevant to informing national policy as well as regional policies in South Asia. For *example*, JiVitA-1 is in the process of assessing the

- Prevalence and epidemiology of 23 types of maternal illness during pregnancy, including obstetrical complications in the peripartum period, through the first six months following childbirth
- Prevalence and epidemiology of infant illnesses through the first six months of life
- Health-seeking behavior and treatment patterns for types and severity of maternal and infant illnesses
- Patterns of infant growth in the first six months of life

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- Incidence, multicausality and demographic patterns of both pregnancy-related and non-pregnancy related mortality of women of reproductive age through standardized conduct and expert review of verbal autopsy questionnaires
- Incidence, multicausality and demographic patterns of infant mortality through the first year of life through conduct and expert review of verbal autopsy questionnaires
- Incidence and epidemiology of spontaneous abortion (miscarriage), menstrual regulation and stillbirth
- Dietary patterns of pregnant and lactating women and their relationship to health, micronutrient status, pregnancy outcome and breast milk nutrient concentration
- Prevalence and epidemiology of sexually transmitted diseases in pregnant and lactating women
- Maternal body compositional status and changes in body composition during pregnancy and lactation
- Apparent prevalence of vitamin K deficiency in mothers and young infants
- Antioxidant status and the potential roles of oxidative stress in maternal illness
- Prevalence of iodine deficiency and potential effects of iodized salt use in preventing iodine deficiency during pregnancy
- Prevalence and epidemiology of birth defects
- Performance of health and nutritional assessment tools, such as a
 - o Revised approach to obtaining a history maternal night blindness
 - o “Home Delivery Card”, maintained and completed by rural family members on which to record times of puerperal events before, during and following childbirth
 - o Physician- and digital-photograph-verified lay surveillance system for detecting birth defects

JiVitA-1 Design and Activities

JiVitA-1 is a cluster-randomized, double-masked, placebo-controlled, community trial, presently taking place in nearly 600 communities, covering an area of 450 sq. km with a population of ~580,000 in 19 selected unions in four thanas of Gaibandha (Sundarganj, Gaibandha, Sadullapur) and Rangpur (Pirgachha) Districts in northwest Bangladesh. The community units, called “sectors”, have been randomized prior to launching the trial for previously registered, newly pregnant women to receive each week one of three types of oral supplements during pregnancy through three months postpartum: a placebo, vitamin A (7000 ug retinol equivalents, RE) or beta-carotene (42 mg in oil, calculated to provide ~7000 ug RE). These amounts approximate recommended dietary intakes for pregnant or lactating women, when calculated on a daily basis of ~1000 ug RE

per day. The nearly 4 million supplements for JiVitA-1 are being periodically batch-produced at RP Scherer Pharmaceuticals in Florida, USA with financial support from the MI/CIDA grant².

From late 2000 through mid-2001, sectors were mapped, households numbered, and consenting married women of reproductive age registered with the JiVitA Project. Commencing August 2001, ~110,000 registered women began to be visited by ~600 trained staff at their homes every five weeks to be screened for pregnancy by menstruation history and, for those reporting to be amenstual, confirmatory urine testing. Following consent, women determined to be pregnant have been enrolled at a rate of ~15,000 per year, assessed for first trimester health status and other risk factors, and given supplements weekly, according to their random sector allocation, through three months after the end of pregnancy. During this period and beyond pregnant women and liveborn infants are followed for vital outcomes. The basic design of the trial is depicted in **Figure 1**. An abbreviated "History of Events" for JiVitA-1 is provided in **Table 1**.

The original sample size estimated for JiVitA-1 to show a 35% reduction in pregnancy-related mortality was 54,000 pregnancies: 18,000 per supplement group. In early 2003, the sample size was increased to 68,000 in order to accommodate a larger than expected proportion of urine-test positive women terminating new pregnancies through menstrual regulation. A lower than expected maternal mortality rate also contributed to the adjusted sample size (from assumed 600 to apparent 500 deaths per 100,000 in the study area). The above the sample size is expected to provide ~45,000 live births, a number that is adequate to detect a 15-20% reduction in 6-month infant mortality. However, based on findings of no effect from NNIPS-2 in Nepal, JiVitA-1 is not expected to produce a major reduction in infant mortality, leading us to consider designing and concurrently implementing the JiVitA-2 newborn supplementation trial (see below).

A substudy of ~3% of enrolled pregnant women, or 500-600 mother-infant pairs in each group living in a contiguous "subsample area" is being followed more intensively for changes in maternal status with respect to vitamin A, beta-carotene and other micronutrients, anemia, body composition, anthropometric size, clinical conditions including general indicators of morbidity and STD infections, intra-uterine and postnatal infant growth, and many other health maternal and infant outcomes that can not be followed in the larger trial.

² Laboratory potency testing services, bottling, labeling, packing and air-freight of supplements from the USA to Bangladesh have been provided without charge by the Access Group, Inc, the parent company of Amway Corporation and the Nutrilite Institute in California, USA, resulting in significant savings to the MI-CIDA grant over past 3 years.

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The JiVitA-1 trial protocol and forms have been reviewed and approved by the Bangladesh Medical Research Council (BMRC) and the Committee on Human Research (CHR) of the Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

As of the end of December 2003, JiVitA-1 has registered 114,287 eligible married women of reproductive age, including a cohort of 11,505 newly pregnant women over the time period. Among this cohort, a total of 36,876 pregnant women have been identified, consented, enrolled and supplemented weekly, representing 98.6% of all identified pregnant women in the study area since enrollment began in August 2001. Approximately 90% of enrolled mothers have taken 90% or more of their intended supplements in the trial, across all three supplemented groups. To-date, among pregnancies that include those that have yet to be completely followed for outcomes, 10,532 have ended through menstrual regulation (56%), spontaneous miscarriage (35%) or stillbirth (9%). This distribution motivated the above increase in sample size. At current rates of recruitment, JiVitA-1 expects to achieve its intended sample size of ~68,000 pregnancies by the late Fall of 2005, with another year required to supplement and follow all remaining pregnant women and their infants through at least three months post partum.

Progress Report for JiVitA-2: Newborn Vitamin A Supplementation Trial to Reduce Infant Mortality

Background

Infant mortality remains exceedingly high throughout South Asia, with published estimates averaging ~75 deaths per 1000 live births for the region and higher rates in most rural populations, including Bangladesh (38). Micronutrient supplementation may reduce infant mortality. One strategy involves providing young infants with vitamin A. While shown to be highly effective in reducing mortality risk when infants are periodically supplemented with vitamin A in the latter half of infancy (39), mixed results makes the benefits of supplementation unclear during the first six months of life (40). Several randomized trials to date, incorporating different study designs, have investigated the survival benefit of supplementing young infants with VA. In NNIPS-1 in Nepal, there was no mortality reduction following VA supplementation of 11,000 infants when dosing was carried out at various ages during the first six months of life (on average, at 2 months of age) (5). A similar lack of effect was noted in a smaller trial in the Western Hills of Nepal (41). In a three-country trial (in India, Ghana and Peru) WHO observed no survival benefit among infants supplemented with 25,000 IU of vitamin A vs. placebo at the time of EPI immunizations at 6, 10 and 14 weeks of age (42). In another trial in southern Nepal, maternal supplementation with a normal dietary amount of vitamin A during and following pregnancy also failed to reduce infant mortality (17). In marked contrast to above findings, two

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randomized trials in Southern Asia have observed mortality to be reduced in infants dosed with vitamin A *shortly after birth*. Thus, Humphrey et al. reported a 64% reduction in mortality among 2067 Indonesian infants dosed with 50,000 IU vs. placebo at birth (5) and, in South India, Rahmathullah et al. have recently observed a 23% reduction in six-month infant mortality in infants receiving 48,000 IU VA vs placebo shortly after birth (32). These findings raise the important possibility that dosing infants with VA at birth or in the first week of life, rather than at ~1 to 4 months of age, can reduce risk of infant mortality in Southern Asia. They suggest that the first few days of life may represent a unique “biological window” of public health importance, during which the lung, immune and other organ systems continue to rapidly develop and mature - processes that may be responsive to supplemental VA and lead to greater protection against potentially fatal infection months later. Equipoise persists, however, amidst the findings of the other trials noted above making the strength of evidence, as well as our understanding of biologic mechanisms, insufficient for developing a public health policy to reduce infant mortality by providing newborns with VA. The JiVitA-2, being launched in January 2004 in Bangladesh, is designed to break the equipoise surrounding this important, policy-relevant question.

Primary Aims

The JivitA-2 trial will address in the context of randomized, double-masked, placebo controlled trial whether a 50,000 IU oral dose of vitamin A delivered to newborn infants in their homes within the first 48 hours of life can reduce six-month infant mortality by at least 15%. Secondly, the trial will examine treatment effects by important modifiers of infant mortality risk, such as gestational age, birth weight and other measures of size at birth, gender, measures of perinatal morbidity and other risk factors not originally being ascertained in infants and mothers as part of JiVitA-1.

JiVitA-2 Design

We propose to address stated aims by conducting a double-masked, placebo-controlled, cluster-randomized newborn oral supplementation trial (called “JiVitA-2”) in both Districts of Gaibandha and southern Rangpur, where the JiVitA-1 trial is presently underway. All sectors for the proposed JiVitA-2 trial have already been defined, mapped, addressed and randomized for consenting pregnant women to continue receiving weekly oral supplements containing a placebo or a recommended dietary allowance of vitamin A or β -carotene from early pregnancy through three months postpartum. This same cohort of pregnant women participating in JivitA-1 will, with their newborns, comprise the study population for JIVitA-2. We will require a sample size of 25,000 live born infants (12,500 in each group) to detect a minimum reduction of 15% in 6-month infant mortality, assuming a control rate of 63 deaths per 1000 live births, after inflating the sample by 26% to account for clustering and loss to follow-up, based on previous trial experiences. However, nesting JiVitA-2 into JiVitA-1 will also offer unique

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opportunities to make several additional comparisons, all with sufficient power to detect between group differences in infant mortality of 25% or more, related to infant receipt or non-receipt of vitamin A in the presence of maternal gestational dosing with placebo, vitamin A or beta-carotene. To realize this 2x3 factorial design, sectors were first stratified by, and then randomized for infants to receive vitamin A or not within maternal supplement codes. The design will permit unique evaluations of the impact of newborn vitamin A receipt alone (among maternal placebo recipients), as well as in the presence of routine maternal vitamin A and beta-carotene supplementation throughout pregnancy and the first three months postpartum.

JiVitA-2 Activities

Mothers will be approached in their home for enrollment into JiVitA-2 during their 3rd trimester of pregnancy. After obtaining informed consent, a 3rd trimester interview will be conducted, consisting of a 30-day history of morbidity, a 7-day dietary and alcohol intake and tobacco use questionnaire, a 7-day household chores questionnaire, and maternal mid arm circumference measurement. Components of the questionnaire are virtually identical to those being already administered to participating mothers during their 1st trimester visit.³ Enrolled women will be followed for child birth (>90% occur at home), after which they will be visited, mostly within 48 hours, by local JiVitA staff who will provide the newborn with a sector-coded, study supplement that will consist of either 50,000 IU VA or placebo in drops of soybean oil. Infant anthropometry (weight, length, mid-upper arm, head & chest circumference) will also be measured within the first few days of life. Enrolled pregnant women and their offspring will be followed weekly through the first three months postpartum and once again at six months post-partum to ascertain infant vital and health status. Infant deaths will be investigated for possible causes by conducting a “verbal autopsy” interview with family members of the deceased to record morbidity and other events leading up to death. Two physicians will independently review verbal autopsy forms to assign causes of death based on algorithms and clinical judgment. The JiVitA Data Safety and Monitoring Board will convene after about half of the intended number of infants has been followed for six months (~13,000) to review interim vital outcome rates by coded group and provide further guidance about conduct of the trial. At the end of the trial, six-month infant mortality rates will be compared between treatment and control groups on an intent-to-treat basis, followed by other stratified and adjusted analyses, as appropriate, that may reveal differential impact of supplementation on infant health and survival by maternal and infant risk factors.

³ JiVitA-1 does not include a 3rd trimester risk factor interview, although this JiVitA-2 procedure will now permit such data to be used for “JiVitA-1” analyses as well.

The JiVitA-2 trial protocol and forms have been reviewed and approved by the Bangladesh Medical Research Council (BMRC) and the Committee on Human Research (CHR) of the Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA. Risks associated with participating in this add-on/nested trial are minimal, consisting of a 3rd trimester maternal risk factor interview and, during the first weekly home visit following childbirth, measuring and giving the study supplement to newborns. Several trials, including three in Bangladesh (43-45) have found risks associated with receipt of 25-100,000 IU of VA in early infancy to be minimal in frequency and severity. The most apparent effect is a transient bulge of the anterior fontanelle (BF), in up to 5% of dosed infants, that usually subsides within 24 to 72 hours (43-48). In Indonesia where 2% of newborns exhibited a BF with the proposed dosage, doppler ultrasonography revealed the bulge to occur without change in either intracranial blood flow or pressure (47). Comorbidity has generally not been observed with a BF following VA receipt. Most studies have shown no other side effects (42,43,47,48) while a few have reported ~2% of VA-dosed infants to show mild, temporary symptoms of irritability or gastrointestinal upset following VA receipt above 6-8% symptomatic rates seen in controls (44,46). Three-year follow-up studies in Indonesia (49) and Bangladesh (50) found no long-term psychomotor, developmental, or growth disadvantages in children who had experienced a BF following VA receipt in early infancy. Thus, mothers will be informed of a small chance of a newborn's soft spot rising that would normally disappear on its own. Visiting staff following birth and dosage receipt will report occurrence of a bulge to on-call JiVitA research physicians who will visit the home, examine the infant, advise, treat or refer, as indicated.

Preparations for launching JiVitA-2 have been underway over the past 8 months such that it is nested into JiVitA-1 without disturbing the latter trial. To do this, additional staff have been added and trained to absorb additional field, administrative, logistical and data management responsibilities in the project sites, while procedures, forms, data entry programs and data management strategies have been developed, tested and prepared for start-up. Vitamin A and placebo capsules have been produced at RP Scherer in Florida, purchased with MI/CIDA grant funds, and bottled, labeled, packed and shipped at not cost to the study by Amway/Nutriline Inc in Buena Park, CA, USA. Supplements have been cleared through customs at Dhaka Airport, transported to the Gaibandha field station, relabeled with study codes, and prepared for issuance to the field. As of mid-January 2004, field teams are undergoing refresher and advanced procedural training. By the end of January, participating JiVitA-1 pregnant mothers entering their estimated 28th week of gestation will be approached by team leaders to obtain consent for their home to be visited shortly after birth, and their newborn assessed and supplemented with the contents of a coded capsule. At 32 weeks' gestation mothers will be interviewed about 3rd trimester risk

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factors, as they also continue to receive their weekly JiVitA-1 coded supplement.

By March 2004, we expect the first births of infants of consenting mothers to occur, which will activate home visits, assessments and supplementation activities that will continue over the next 2 ½ years (ending field work by November 2006).

Plans for JiVitA-3: Maternal Multiple Micronutrient Supplementation Trial to Reduce Low Birth Weight and Infant Mortality

At present JiVitA-3 is strictly in the planning stages, with the composition of possible antenatal micronutrient combinations to test and outcomes to specifically evaluate presently being informed by ongoing analyses of the NNIPS-3 5-arm antenatal micronutrient supplementation trial that was recently completed in Nepal (25,28,29). We anticipate starting up JiVitA-3 in late 2005, with a likely sample size of 36,000 pregnant women.

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Expenditures from MI/CIDA Grant: February 2001 – December 2003

The initial motive for entering into a contractual agreement with for the JiVitA Bangladesh studies was to provide funds for supplements and related activities, for which a budget of CAD 646,800 was agreed (USD \$420,000 at an approximate year 2001 exchange rate of CAD 1.00 = USD 0.64935). Existing conditions governing the current MI/CIDA grant to JHU are provided in the "*Restated Memorandum of Grant Conditions*", to Dr. Keith P. West, Jr., dated 25 January 2001. At the time the grant was for a 3-year period, during which time it was anticipated that all funds would be expended for trial supplements and associated activities. A first payment equivalent to USD 177,715.28 was made in March 2001. However, several issues arose that have made it impossible to spend the funds on costs strictly related to supplements and their use, as originally planned. Specifically, at the time of the original grant, it was anticipated that JiVitA would require more supplements than needed for the 1st three years of work, due to the planned, more immediate start-up of a large *daily* micronutrient supplement trial, that has since evolved into JiVitA-3, still not due to begin for another 2 years.

JiVitA-1 was redesigned for *weekly* rather than daily vitamin A, beta-carotene or placebo supplement use, reducing the number of supplements needed by 6/7ths. Start-up of JiVitA-1 also did not begin for 6 months following award of the grant, causing delays in flow of supplements in relation to the time period of the grant. Finally, as the grant was being finalized, the Amway/Nutriline Institute of the Access Business Group kindly decided to donate all supplement testing, bottling, labeling and overseas air freight costs, for which grant funds would have been used.

Thus, changes in strategy from concurrent to sequential studies, delays in start-up, reduced immediate demand for original numbers of supplements, coupled with significant cost savings from other sources, have led to significant underspending of grant funds. This has been a paradoxical situation for JHU because, at the same time the JiVitA research program faces numerous financial demands and obligations in running this major activity for which broader and more flexible MI/CIDA support through the grant would be of tremendous help.

As a result, during the first 35 months of MI/CIDA-supported JHU-JiVitA research activity in Bangladesh, only US\$125,951 (71%) of the initial year's installment of US\$177,715.28 has been expended, as described in **Table 2** and explained as follows:

Field Personnel: \$21,588

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JHU: Partial (~2%) salary support for three (3) JHU personnel resident in Bangladesh providing full-time technical oversight to the field trial and supplementation activities

Local Staff: Partial (~3%) salary support for local staff who are directly involved with the storing, logging, distributing, replenishing and documenting capsules and capsule receipt.

Travel: \$8,626

International: Two roundtrip airfares and related expenses from Baltimore to Bangladesh, one each for the Principal Investigator and a co-investigator to provide essential technical input for planning capsule storage, inventory and distribution systems.

Facilities: \$2,498

Partial rental fees for premises in which supplements are stored, comprising a central field station in which the supplements are climate controlled.

Supplements: \$83,016

JiVitA-1: Production costs for two batches of 1.2 million capsules or a total of 2.4 million supplements, one-third containing ~23,000 IU vitamin A, one-third containing 42 mg of beta-carotene and one-third containing soybean oil and a small amount of vitamin E (\$73,016).

JiVitA-2: Production costs for one-batch of supplements, 25,000 of which contain 50,000 IU vitamin A and 25,000 of which contain soybean oil and a small amount of vitamin E (\$10,000).

Administrative Fee: \$10,233

Administrative fee (10%) charged by JHU to maintain and manage grant funds and activities supported by the grant.

No direct or indirect costs for JHU salaries (other than the small percentage of level of effort for field investigators), or on-campus expenses have been charged to the grant. The resulting current balance unspent from the first installment is US\$ 51,003.64. In terms of funds available from the entire grant, there remains a total of US\$ 294,049.

Note from Erick Boy: An additional amount has been spent on capsule procurement since this report was submitted. NO other expenses were approved since then as this grant is exclusively for supplement procurement.

Proposed JHU-JiVitA Activity Plan and Budget: January 2004 – June 2004

Given (1) the short (6-month) time period remaining for the MI/CIDA grant, (2) the small amount of expenditures to-date supported by the grant, (3) that no further supplement purchases are required during the remaining eligible grant period, (4) and an ongoing and increasing financial needs to support the many activities of JiVitA (5) in the face of continuous pressures on the part of the existing primary funding Agency to trim budgets without sacrificing quality and standards of research, we propose that the MI/CIDA grant support major direct cost components of JiVitA field operations for the six-month period extending from 1 January through 30 June 2004, as outlined in **Table 3**. This support would be greatly appreciated and serve to assure the MI/CIDA of clear credit for supporting both JiVitA-1 and JiVitA-2 on all future publications emerging from these two major trials, since both will be underway during this six month period. Given the track record of reporting research findings from the NNIPs trials, we anticipate no fewer than 30 scientific publications from the two current JiVitA trials following their completion.

The direct costs associated with implementing the JiVita-1 and JiVita-2 maternal and newborn supplementation trials averages US \$55,000 per month. Approximately 75%, or about US \$42,000, of the monthly operating costs supports the Project's 770 Bangladeshi field, technical, administrative, data management professional and logistical support staff who are based in 70 field offices, a field station and a data management/study headquarters facility located across the study area. Therefore, we ask that the MI/CIDA grant support the JiVitA payroll for the 6-month period, amounting to approximately US \$252,000. Approximately 65% of this payroll can be attributed directly to field operations where the primary responsibility lies for delivering supplements to both mothers and infants in each respective trial. In addition, we ask the grant to support monthly travel costs in the field related to staff per diem, various allowances and travel expenses that amount to ~\$1300 per month. Most of these travel costs relate to activities that directly support transport, delivery, supervision and documentation of supplement receipt in each trial. Finally, we ask the grant support our monthly transport expenses, that amount to ~US \$ 1500 per month. These costs are attributed to purchase of fuel, oil, repairs, regular maintenance, replacement, and other charges associated with operating a fleet of 136 bicycles, 48 motorcycles and 3 Toyota LandCruisers which, in total, ply ~60,000 km each month. The total monthly direct costs to support these specific needs is US \$44,800, or US \$268,800 over the six-month period, as listed in Table 3. The amount represents ~81% of the monthly direct costs, unassociated with JHU in-country staffing, for a six month period.

In view of the special nature of this request, involving increased expenditures over a shorter period of time, we propose to decrease the administrative fee from

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10% to 6%, for a total of US \$16,128, so that a larger percentage of the funds can be directly applied to field costs.

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Table 1. Brief History of JiVitA Bangladesh Trial Activities

Landmark Activity/Event in Developing JiVitA	Date Achieved
Initial exploratory visit by JHU faculty to Bangladesh to establish initial in-country collaboration with BIRPERHT, a parastatal reproductive health institution, and to meet with USAID Mission in Dhaka to discuss national importance of a maternal micronutrient research program	February 1998
Meetings with Secretary of Ministry of Health & Family Welfare (MOHFW), Government of Bangladesh (GOB) to discuss maternal and infant nutrition research priorities and proposed initial trials involving maternal vitamin A and beta-carotene and multiple micronutrient supplementation in Bangladesh	November 1998
Districts of Gaibandha and Rangpur Study selected as study area that represented the “~25%ile” on many national characteristics, following site visits throughout the country and evaluations of available national, regional and local data on health and development	November 1998
USAID Mission expresses formal interest in the proposed trial in writing to the MOHFW	December 1998
National Technical Committee (NTC) is established by the Secretary for Health in the MOHFW; several meetings held to consider, discuss and eventually approve technical content of the proposed trials to test impact of maternal vitamin A or beta-carotene, as well as multiple micronutrient, supplementation	February to July 1999
Study protocol for first maternal vitamin A or beta-carotene trial, including disclosure statements and draft forms submitted to Bangladesh Medical Research Council (BMRC) for ethical review	August 1999
First formal “Implementation Agreement” signed between BIRPERHT, on behalf of the JiVitA Project and JHU, and the MOHFW of the GOB	September 2000

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Rural study area of 450 sq km with total population of 580,000 mapped; over 130,000 households located and addressed with study numbers; 596 community "sectors" defined (as units of randomization)	April to October 2000
Study organization and management established; nearly 600 local female field distributors, initial 36 female interviewers, 18 data center staff, and over 50 other professional, technical administrative personnel recruited, hired, trained and standardized	November 2000-June 2001
JiVitA-1 study protocol submitted to JHU Committee on Human Research (CHR) for ethical review; JiVitA Calendar established (first week of January designated "JiVitA Week 001")	January 2001
Canadian International Development Agency grant awarded to JHU to support purchase and use of micronutrient supplements in JiVitA trials	February 2001
First batch of study supplements produced, bottled, labeled and shipped from USA to Bangladesh; Study sectors randomized for pregnant women enrolled in the future to receive one of 3 supplement codes (placebo, vitamin A or beta-carotene)	May 2001
Study protocol approved by BMRC	May 2001
Study protocol approved by the JHU CHR	May 2001
Study sectors (n=596) surveyed and profiled for major characteristics	June 2001
Over 100,000 married women of reproductive age enumerated and registered with JiVitA	July 8-August 5, 2001 (JiVitA Weeks 028-032)
Five weekly, community-based pregnancy surveillance with urine-test verifications initiated in the study area	August 12, 2001 (JiVitA Week 033)
Supplementation of consenting pregnant women by randomized treatment code begun	August 19, 2001 (JiVitA Week 034)
JiVitA Project, with concurrence and assistance from the USAID Mission and MOHFW, became formally	May 2002

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 registered as a project under the bilateral National
 Integrated Population and Health Program (NIPHP) of
 the Governments of Bangladesh & United States

JiVitA-1 "Substudy", an enriched set of clinical, biochemical, anthropometric, dietary, infectious diseases and functional maternal and infant assessment protocols carried out in a smaller area across sectors for all 3 supplement groups, nested into southern part of the larger trial area, is launched	July 2002
JiVitA-1 sample size increased from 54,000 to ~68,000 pregnancies due to higher than initially expected numbers of menstrual regulations and miscarriages early in gestation	March 2003
JiVitA GIS mapping system, after two years of experimental development, is launched; the GIS system is expected to convey numerous advantages for managing the trials, conducting epidemiologic investigations throughout the study area	June-July 2003
JiVitA-1 data set frozen for first Data and Safety Monitoring Board (DSMB) meeting, scheduled and held later in the year (November 2003)	June 30, 2003 (JiVitA Week 130)
First Data Safety and Monitoring Board meeting convened; trial judged to be procedurally correct and, based on data analysis, trial recommended to continue	November 2-4, 2003
Enrollment of pregnant women for JiVitA-1 reaches the half-way mark of 34,000 pregnant women	November 2003
JiVitA trial organization reaches a size of over 750 trained field, administrative, data management, logistical and professional staff, as it prepares to launch JiVitA-2 newborn vitamin A supplementation trial in the first quarter of 2004, while maintaining the JiVitA-1 maternal supplementation trial in full operation	January 2004
Launch of the JiVitA-2 randomized, placebo-controlled, newborn vitamin A supplementation trial; expected sample size ~26,000 live born infants	January 2004

Table 2. Financial Report for Micronutrient Supplementation Trials in Bangladesh: Centre/MI filed: 5600-0007-02-300⁴

JHU Cost Category	March 2001 - Dec 2003
Field personnel	
JHU	13,501.00
Local staff	8,087.00
Subtotal	21,588.00
Travel	
International (2)	8,626.00
Subtotal	8,626.00
Transportation	-
Subtotal	-
Facilities (storage)	2,498.00
Subtotal	2,498.00
Supplements	
JiVitA-1	73,016.00
JiVitA-2	10,000.00
Subtotal	83,016.00
Laboratory	-
Subtotal	-
Equipment	-
Subtotal	-
Other expenses	-
Subtotal	-
Total Field Expenses	115,718.00
Administrative Fee (10%)	10,233.00
Direct Total Expenditures	125,951.00
Award obligation to date	77,715.28
Unspent pipeline to date	51,764.28
Total award *	420,000.00
Award obligation to date	177,715.28
Expenditures to date	125,951.00
Unobligated	242,284.72
Total unspent to date	294,049.00

Comment: Was this allowed under current GRANT agreement????

⁴ Total award of US \$420,000 is calculated from the original grant of CAD 646,800 stated in the "Restated Memorandum of Grant Conditions" dated January 25, 2001, based on an approximate years 2001 exchange rate of 1 USD = 0.64935 CAD.

Table 3. Proposed Budget Expenditures for Micronutrient Supplementation Trials in Bangladesh, 1 January to 30 June 2004: Centre/MI filed: 5600-0007-02-300

Cost Category	Estimated Proposed Monthly Expenditure Jan - June 2004	Six-Month Expenditure Total
Field personnel		
JHU	-	
Local staff 600 local distributing supplements 56 in interviews on supplement effects 70 in direct supervision of operations 20 data management staff 12 rest if administrative 9 professional staff	42,000	252,000
Travel, local	1300	7,800
Transportation, local	1500	9,000
Facilities	-	
Supplies	-	
Laboratory	-	
Equipment	-	
Other expenses	-	
Total Expenses	44,800	268,800
Administrative Fee (5%)	2688	16,128
Direct Total Expenditures	47,488	284,928 – 51,000 USD in hand

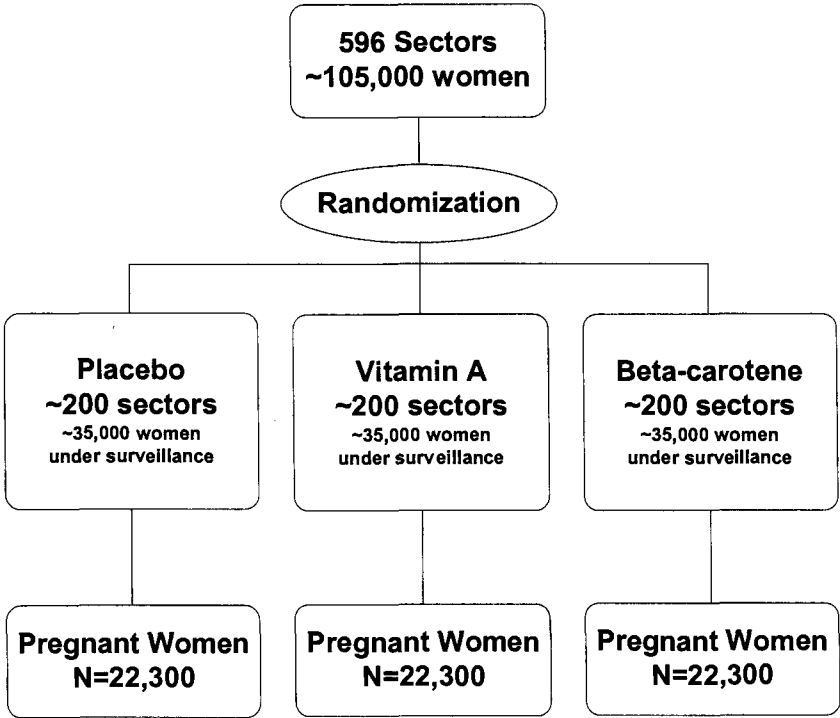


Figure 2. Map of JiVitA-1 Study Area

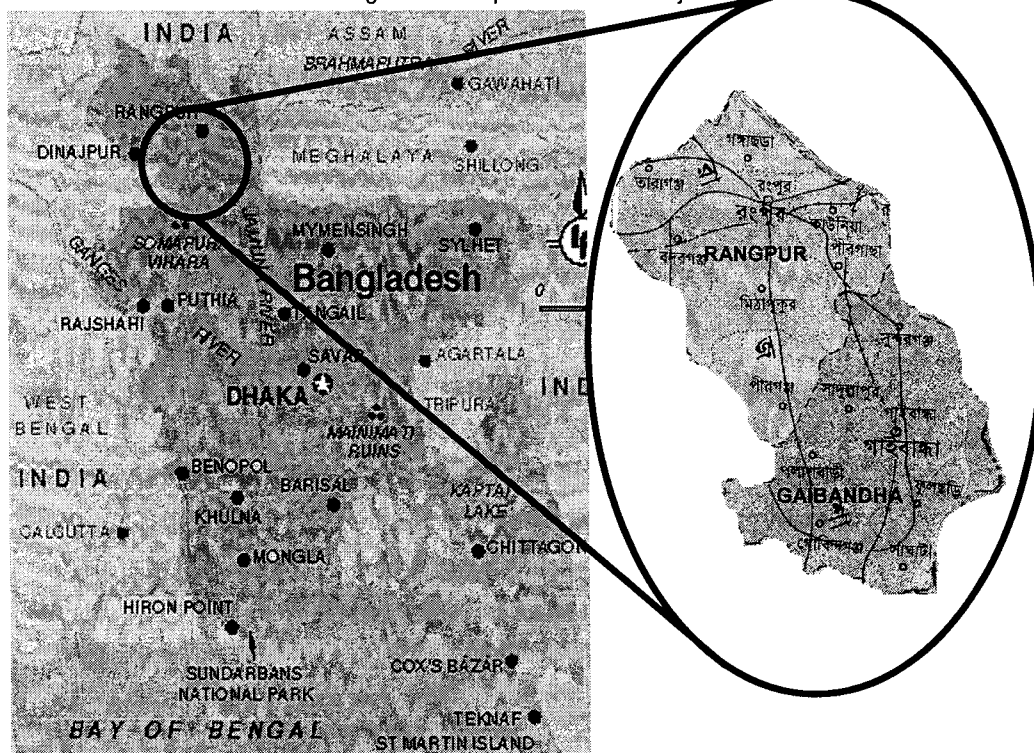
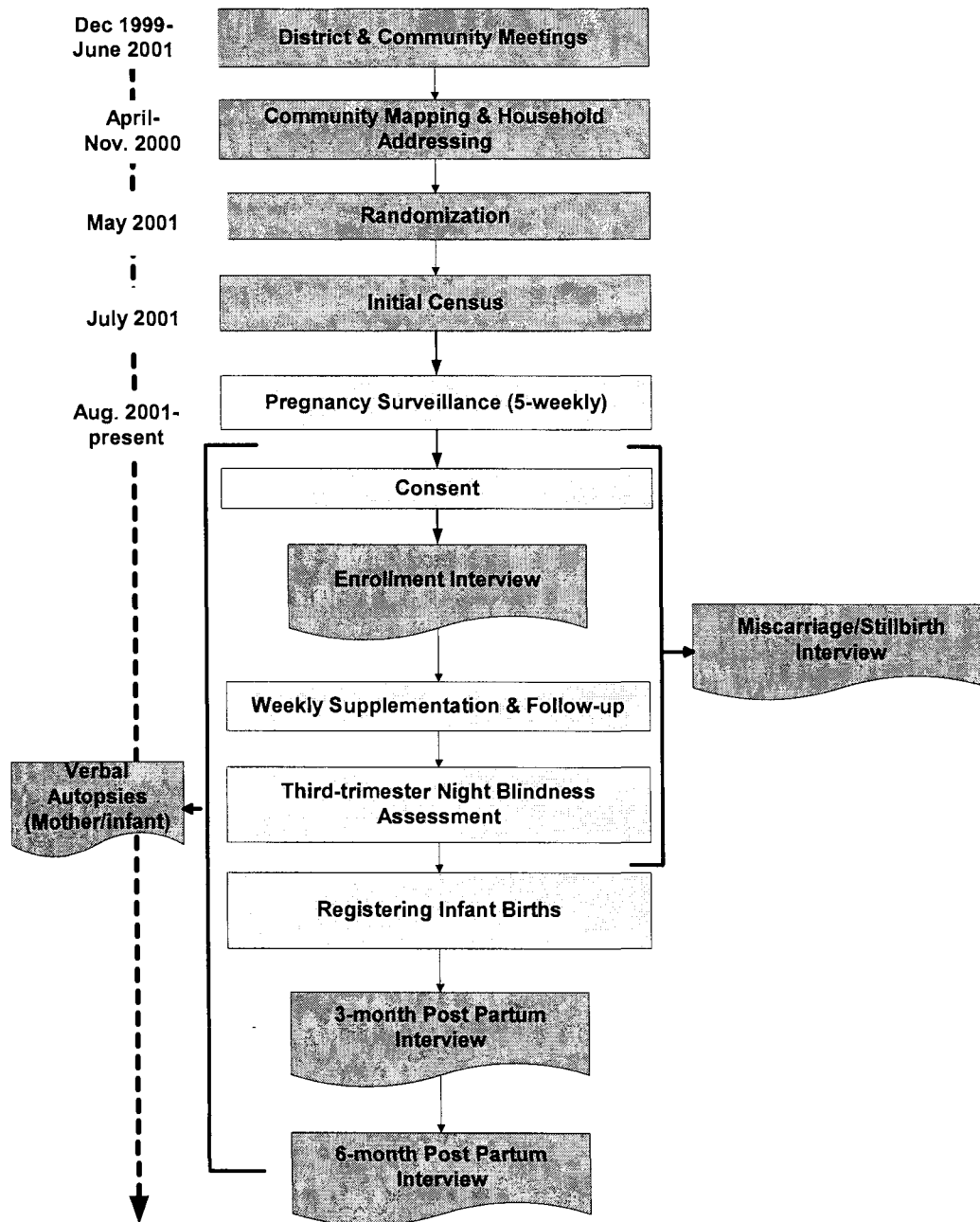


Figure 3. Diagram of JiVitA-1 Procedures and Timeline



**Maternal and Infant Micronutrient
Research Program in Bangladesh
Centre/MI File: 5600-0007-02-300**

**Technical Report and
Proposed Activity Plan and Budget**

submitted to

**The Micronutrient Initiative/
Canadian International Development Agency
Ottawa, Canada**

January 2004

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Executive Summary

JiVitA is a collaborative¹ research project dedicated to determining the efficacy of micronutrient and other practical nutritional approaches to improving the health and survival of mothers, infants and children in rural Bangladesh and, more broadly, in the South Asian Region. JiVitA also enjoys collaboration in its research and training activities with several national, regional and international centers, including the Institute of Nutrition, University of Dhaka; the National Institute for Preventive and Social Medicine (NIPSOM), Dhaka; the International Atomic Energy Agency (IAEA) through the Bangladesh Atomic Energy Commission (BAEC) in Dhaka, Bogra and Rangpur; the Rangpur Medical Center (RMC), Rangpur; the Institute for Child and Maternal Health (ICMH), Dhaka; and the Institute of Nutrition at Mahidol University (INMU), Salaya Campus, Thailand.

JiVitA further shares a unique relationship with another large, population-based nutrition and health research activity in the region, its sister public health research project - the Nepal Nutrition Intervention Project-Sarlahi (NNIPS), with a trained staff of ~550 working in a population of nearly 300,000 people. Together, NNIPS and JiVitA have completed or are presently carrying out seven micronutrient intervention trials that have enrolled, supplemented and followed over 130,000 infants and preschool children and nearly 120,000 women of reproductive age, with more than 60 scientific publications to date having emerged from NNIPS alone addressing effects of vitamin A, beta-carotene, folic acid, iron, zinc and other micronutrients on child and maternal survival, health and function (eg, see refs 1-30). The ability to communicate and coordinate visions, goals, plans, protocols, procedures, administrative policies and other activities between JiVitA and NNIPS enables these two research projects, working in a combined rural South Asian population of nearly 1 million, to “feed off one another” and accelerate research on key nutrition and health priorities and provide stronger policy evidence for interventions in South Asia.

Established in January 1998, and now operating in a rural population of ~580,000 in the Districts of Gaibandha and Rangpur in northwestern Bangladesh, the Project seeks to evaluate the efficacy and safety of micronutrient and other nutrition interventions through the conduct of intervention trials and epidemiological studies, training, providing technical assistance and offering policy guidance related to nutrition interventions nationally and within the region.

Establishing the JiVitA Bangladesh research project and setting of its initial goals has been motivated by findings from several NNIPS trials in recent years that revealed the potential for maternal dietary supplementation with (1) vitamin A or beta-carotene to

¹ JiVitA is a joint undertaking by the Center for Human Nutrition, Department of International Health of the Johns Hopkins University Bloomberg School of Public Health, Baltimore MD, USA (JHU) and the Ministry of Health and Family Welfare (MOHFW) of the Government of Bangladesh (GOB) under the National Integrated Health and Population Program (NIPHP) of the MOHFW, GOB and the US Agency for International Development (USAID), Dhaka. JiVitA is primarily funded by the Office of Health, Infectious Diseases and Nutrition and the Bangladesh Mission of the US Agency for International Development (USAID), Washington DC and Dhaka, most recently as part of a new “Global Research Activity” (GRA) grant to the Department of International Health at JHU, and by the Bill and Melinda Gates Foundation, Seattle, WA.

markedly reduce risk of mortality related to pregnancy (16), (2) folic acid and iron to reduce risk of low birth weight and infant mortality but with (3) a multiple micronutrient combination to improve birth weight without commensurate effects on infant survival (25,29). JiVitA has also drawn direction from two other JHU sister projects, in Indonesia in the mid-nineties (31) and, more recently from Tamil Nadu in southern India (32), that have shown supplementation with vitamin A *at birth* to markedly reduce risk of infant mortality. The findings of these trials have stimulated enormous interest to affirm and extend knowledge of these effects, and to provide the required evidence for developing the most beneficial, safe and appropriate combinations of micronutrients for routine maternal, infant and child use in the South Asian region.

Thus, the JiVitA Project has, at present, three major research aims to address in a previously not-studied, large, rural population in Bangladesh:

- Estimate the impact of maternal, low-dose vitamin A or beta-carotene supplementation on mortality related to pregnancy (JiVitA-1);
- Estimate the impact of administering a single large dose of vitamin A to newborns on infant mortality (JiVitA-2);
- Test effects of alternative combinations of supplemental antenatal micronutrients on intrauterine growth, preterm delivery, fetal loss and infant mortality (JiVitA-3).

Briefly:

JiVitA-1 (maternal low dose VA or B-carotene and mortality related to pregnancy) began in August 2001. Its intended sample size is 68,000 pregnant women. Enrollment is planned to be complete by November 2005 and all fieldwork finished by December 2006.

JiVitA-2 (single large dose of VA to newborns) is being launched in January 2004 with an intended sample size of 26,000 live born infants. Enrollment is planned to finish by March and field work completed by December 2006.

JiVitA-3 (different antenatal MN supplements) is currently being planned to start by December 2005 with a planned sample size of 36,000 pregnant women. Enrollment is expected to be completed by December 2007 and field work by December 2008.

With in-country negotiations starting in January 1998, and following 3 ½ years of development, the JiVitA Project launched its first, currently ongoing JiVitA-1 maternal vitamin A and beta-carotene supplementation trial in August 2001. Presently, the Project maintains a 5-weekly, home-based, hcg urine test pregnancy surveillance system among ~110,000 married women living in 596 communities (sectors); all communities have been mapped and 130,000 households addressed and registered in a project GIS system; JiVitA-1 enrolls, supplements and follows ~15,000 pregnancies each year. In a substudy area, each year the project carries out enhanced assessment protocols on ~600 mothers and their infants, including gestational and post-partum phlebotomy, clinical examinations, body composition assessment, diagnostic tests for STDs, proteinuria and diabetes, dietary and behavioral evaluations, measurement of birth size and infant growth

rates, among other assessments in order to enrich impact data on potential mechanisms of supplement action and to reveal risks and qualities of life within this typical, rural Bangladeshi study population. The data entry center in Rangpur processes and enters onto the computerized database about 25,000 records each month.

To perform this work, as of January 2004, the JiVitA Project employs approximately 770 staff, including ~680 local women who have been hired and trained into field distributor, interviewer, supervisory, quality control, data management and administrative positions. The Project is served by a full-time Bangla research team of 10 physicians, nutritionists, epidemiologists and social scientists and a full-time JHU team of 9 investigators and technical staff, 3 of who are resident in Bangladesh. The Project has two national advisors and a national technical committee 12 prominent health scientists organized under the Secretary for Health within the MOHFW. Each year Project activities are reviewed and approved under the GOB-USAID National Integrated Population and Health Program.

Additional funding is gratefully acknowledged from the Micronutrient Initiative, Ottawa, Canada that has been provided, to date, specifically for the purchase and support activities related to distribution of micronutrient supplements within the JiVitA Project. Additional limited resources have been received from the Sight and Life Research Institute, Baltimore, MD, and the Nutrilite Division of the Access Business Group LLC, Buena Park, CA, USA.

2. Expenditures from MI/CIDA Grant: February 2001 – December 2003

The initial motive for entering into a contractual agreement with for the JiVitA Bangladesh studies was to provide funds for supplements and related activities, for which a budget of CAD 646,800 was agreed (USD \$420,000 at an approximate year 2001 exchange rate of CAD 1.00 = USD 0.64935). Existing conditions governing the current MI/CIDA grant to JHU are provided in the “*Restated Memorandum of Grant Conditions*”, to Dr. Keith P. West, Jr., dated 25 January 2001. At the time the grant was for a 3-year period, during which time it was anticipated that all funds would be expended for trial supplements and associated activities. A first payment equivalent to USD 177,715.28 was made in March 2001. However, several issues arose that have made it impossible to spend the funds on costs strictly related to supplements and their use, as originally planned. Specifically, at the time of the original grant, it was anticipated that JiVitA would require more supplements than needed for the 1st three years of work, due to the planned, more immediate start-up of a large *daily* micronutrient supplement trial, that has since evolved into JiVitA-3, still not due to begin for another 2 years.

JiVitA-1 was redesigned for *weekly* rather than daily vitamin A, beta-carotene or placebo supplement use, reducing the number of supplements needed by 6/7ths. Start-up of JiVitA-1 also did not begin for 6 months following award of the grant, causing delays in flow of supplements in relation to the time period of the grant. Finally,

as the grant was being finalized, the Amway/Nutriline Institute of the Access Business Group kindly decided to donate all supplement testing, bottling, labeling and overseas air freight costs, for which grant funds would have been used.

Thus, changes in strategy from concurrent to sequential studies, delays in start-up, reduced immediate demand for original numbers of supplements, coupled with significant cost savings from other sources, have led to significant underspending of grant funds. This has been a paradoxical situation for JHU because, at the same time the JiVitA research program faces numerous financial demands and obligations in running this major activity for which broader and more flexible MI/CIDA support through the grant would be of tremendous help.

As a result, during the first 35 months of MI/CIDA-supported JHU-JiVita research activity in Bangladesh, only US\$125,951 (71%) of the initial year's installment of US\$177,715.28 has been expended, as described in **Table 2** and explained as follows:

Field Personnel: \$21,588

JHU: Partial (~2%) salary support for three (3) JHU personnel resident in Bangladesh providing full-time technical oversight to the field trial and supplementation activities

Local Staff: Partial (~3%) salary support for local staff who are directly involved with the storing, logging, distributing, replenishing and documenting capsules and capsule receipt.

Travel: \$8,626

International: Two roundtrip airfares and related expenses from Baltimore to Bangladesh, one each for the Principal Investigator and a co-investigator to provide essential technical input for planning capsule storage, inventory and distribution systems.

Facilities: \$2,498

Partial rental fees for premises in which supplements are stored, comprising a central field station in which the supplements are climate controlled.

Supplements: \$83,016

JiVitA-1: Production costs for two batches of 1.2 million capsules or a total of 2.4 million supplements, one-third containing ~23,000 IU vitamin A, one-third containing 42 mg of beta-carotene and one-third containing soybean oil and a small amount of vitamin E (\$73,016).

JiVitA-2: Production costs for one-batch of supplements, 25,000 of which contain 50,000 IU vitamin A and 25,000 of which contain soybean oil and a small amount of vitamin E (\$10,000).

Administrative Fee: \$10,233

Administrative fee (10%) charged by JHU to maintain and manage grant funds and activities supported by the grant.

No direct or indirect costs for JHU salaries (other than the small percentage of level of effort for field investigators), or on-campus expenses have been charged to the grant.

The resulting current balance unspent from the first installment is US\$ 51,003.64. In terms of funds available from the entire grant, there remains a total of US\$ 294,049.

Proposed JHU-JiVitA Activity Plan and Budget: January 2004 – June 2004

Given (1) the short (6-month) time period remaining for the MI/CIDA grant, (2) the small amount of expenditures to-date supported by the grant, (3) that no further supplement purchases are required during the remaining eligible grant period, (4) and an ongoing and increasing financial needs to support the many activities of JiVitA (5) in the face of continuous pressures on the part of the existing primary funding Agency to trim budgets without sacrificing quality and standards of research, we propose that the MI/CIDA grant support major direct cost components of JiVitA field operations for the six-month period extending from 1 January through 30 June 2004, as outlined in **Table 3**. This support would be greatly appreciated and serve to assure the MI/CIDA of clear credit for supporting both JiVitA-1 and JiVitA-2 on all future publications emerging from these two major trials, since both will be underway during this six month period. Given the track record of reporting research findings from the NNIPs trials, we anticipate no fewer than 30 scientific publications from the two current JiVitA trials following their completion.

The direct costs associated with implementing the JiVita-1 and JiVitA-2 maternal and newborn supplementation trials averages US \$55,000 per month. Approximately 75%, or about US \$42,000, of the monthly operating costs supports the Project's 770 Bangladeshi field, technical, administrative, data management professional and logistical support staff who are based in 70 field offices, a field station and a data management/study headquarters facility located across the study area. Therefore, we ask that the MI/CIDA grant support the JiVitA payroll for the 6-month period, amounting to approximately US \$252,000. Approximately 65% of this payroll can be attributed directly to field operations where the primary responsibility lies for delivering supplements to both mothers and infants in each respective trial. In addition, we ask the grant to support monthly travel costs in the field related to staff per diem, various allowances and travel expenses that amount to ~\$1300 per month. Most of these travel costs relate to activities that directly support transport, delivery, supervision and documentation of supplement receipt in each trial. Finally, we ask the grant support our monthly transport expenses, that amount to ~US \$ 1500 per month. These costs are attributed to purchase of fuel, oil, repairs, regular maintenance, replacement, and other charges associated with operating a fleet of 136 bicycles, 48 motorcycles and 3 Toyota LandCruisers which, in total, ply ~60,000 km each month. The total monthly direct costs to support these specific needs is US \$44,800, or US \$268,800 over the six-month period, as listed in Table 3. The amount represents ~81% of the monthly direct costs, unassociated with JHU in-country staffing, for a six month period.

In view of the special nature of this request, involving increased expenditures over a shorter period of time, we propose to decrease the administrative fee from 10% to 6%, for a total of US \$16,128, so that a larger percentage of the funds can be directly applied to field costs.

Table 3. Proposed Budget Expenditures for Micronutrient Supplementation Trials in Bangladesh, 1 January to 30 June 2004: Centre/MI filed: 5600-0007-02-300

Cost Category	Estimated Proposed Monthly Expenditure Jan - June 2004	Six-Month Expenditure Total
Field personnel		
JHU	-	
Local staff 600 local distributing supplements 56 in interviews on supplement effects 70 in direct supervision of operations 20 data management staff 12 rest if administrative 9 professional staff	42,000	252,000
Travel, local	1300	7,800
Transportation, local	1500	9,000
Facilities	-	
Supplies	-	
Laboratory	-	
Equipment	-	
Other expenses	-	
Total Expenses	44,800	268,800
Administrative Fee (5%)	2688	16,128
Direct Total Expenditures	47,488	284,928 – 51,000 USD in hand

RESTATED MEMORANDUM OF GRANT CONDITIONS

The International Development Research Centre (the Centre), acting on behalf of the Micronutrient Initiative (MI), hereinafter referred to as "the Centre/MI", has approved a grant in an amount of up to \$646,800 CAD to

Johns Hopkins University

(hereinafter called "JHU")

to enable JHU to undertake, with the following key national collaborating agency:

Bangladesh Institute of Research for Promotion of Essential and Reproductive Health and Technologies (BIRPERHT)

(hereinafter called "Collaborating Agency")

the research project entitled "JiVitA-Maternal Vitamin A and Micronutrient Supplementation Trial in Bangladesh" described in Section 1 of this Memorandum (hereinafter called "Project").

It is understood that JHU is responsible for informing the Collaborating Agency to adhere to the conditions and terms stipulated in this Restated Memorandum of Grant Conditions.

JHU will provide the Centre/MI with a letter from the above Collaborating Agency, in which the Collaborating Agency acknowledges receipt of a copy of this agreement and agrees to comply with its terms and conditions which may apply, specifically those related to ethical considerations of the Project, set out below in section 12 of this Memorandum.

The grant is subject to sufficient funds being made available to the Centre/MI by the Parliament of Canada during the full course of the grant.

GRANT CONDITIONS

JHU agrees that the payment of any funds under this grant is subject to its compliance with the conditions set out in this Memorandum.

1. Components and Objectives of Project

The overall objective of the research Project is to establish the public health importance of an adequate maternal intake of vitamin A and other essential micronutrients in improving maternal, fetal and infant health and survival in rural Bangladesh. The recipient proposes to do this by delivering, to women, daily/weekly dietary supplements containing recommended amounts of these micronutrients during pregnancy through 3 months postpartum.

The specific objectives of the Project are as follows:

- a) to determine whether maternal supplementation with either vitamin A alone or multiple micronutrients (that also contain vitamin A) during pregnancy through the first 3 months postpartum, at recommended levels, reduces mortality related to pregnancy by at least 35%; and
- b) to establish the impact of maternal vitamin A or multiple micronutrient use during pregnancy and postpartum periods on:
 - . fetal loss due to miscarriage or still birth;
 - . infant mortality under 3 months of age;
 - . maternal obstetric and infectious morbidity;
 - . infant infectious morbidity;
 - . maternal and infant micronutrient status;
 - . intrauterine growth and prematurity; and
 - . postnatal infant growth to 3 months of age.

2. Administration of Grant

The grant funds will be provided to JHU as follows:

Initial Payment

Upon receipt by the Centre/MI of a copy of this Memorandum duly signed by JHU

\$274,890 CAD

JHU will forward to the Centre/MI satisfactory technical reports and financial statements on the Project which reflect the use of Centre/MI grant funds at the following intervals as a condition for receiving subsequent payments:

First Technical Report and Financial Statement

Twelve months after acceptance

Second Technical Report and Financial Statement

Twenty-four months after acceptance

Final Technical Report and Financial Statement

Upon completion of the Project

Note: The third payment (which will be 24 months after acceptance) will also be dependent on the mid-term assessment report to be filed pursuant to section 12(h) (It applies to the use of its remaining funds in the grant).

The financial statement will be prepared in a format similar to the attached Budget and will be signed by the Project Leader and by a senior financial officer of JHU and will include:

- a) a certification, in US dollars, of the amount of Centre/MI grant funds expended on the Project to the statement date, and
- b) an estimate of expenditures, in US dollars, for the following payment period.

The actual timing and amount of payments in annual instalments will be dependent on receipt of the required reports and the estimated financial needs.

The Centre/MI will retain 15% of the estimated financial needs of the final year, until receipt of the technical report and financial statement described in section 8. The amount of the final payment will take into account the actual expenditures of the Project.

3. Grant Budget

JHU will expend the grant funds approximately in accordance with the attached Budget (which forms an integral part of this Memorandum), and will consult with the Centre/MI and obtain its consent prior to any substantial change in budgetary allocations.

4. Compliance with National Laws

In carrying out this Project, JHU will be responsible for complying with all applicable laws and regulations of Bangladesh.

5. Disclaimer

JHU undertakes the Project on its own behalf and not on behalf of the Centre/MI and the Centre/MI grant shall in no way be construed as creating the relationship of principal and agent, of partnership in law or of joint venture as between the Centre/MI and JHU or any other person involved in the Project.

The Centre/MI assumes no liability with respect to any accident to any person or any loss or damage to any person or property arising from the Project except with respect to any accident, loss or damages arising from the negligent acts or omissions of the Centre/MI's employees, officers or agents acting within the scope of their employment or authority.

6. Importation

JHU is responsible for undertaking all formalities and other administrative arrangements necessary for the importation into Bangladesh, of any material, equipment or goods purchased with Centre/MI funds for the Project. It will also take all necessary steps to ensure that grant funds are not used for the direct payment of custom, import or other duties or taxes levied with respect to such importation.

In particular, JHU will take full responsibility for securing importation of caplets purchased with grant funds into Bangladesh as a tax-free commodity, without commercial value; failing which, JHU will bear full responsibility for custom, import or other duties or taxes which may be levied.

7. Procurement

JHU will use its own procurement policies and practices in the purchase of caplets for purposes of the supplementation trial.

8. Final Report and Certification

Upon completion of the Project, JHU will provide the Centre/MI with:

- a) a technical report that is a summary report of the results for the whole project (but not detailed data of the whole study), in printed form (two copies), and, in addition, when possible, a machine-readable copy of the report, on diskette, specifying the hardware and software(s) used; and
- b) a complete financial statement, in US dollars, covering all funds expended on the Project, in the same form and including the detail of the Budget attached to this Memorandum. The financial statement shall be certified correct by the Project Leader and by a senior financial officer of JHU.

JHU agrees that, if the Centre/MI so requests, the final financial statement shall be certified by JHU's external auditors and the cost of such audit shall be borne by the Centre/MI.

9. Visits to Project

JHU, at the request of the Centre/MI, will permit officers or representatives of the Centre/MI to visit the Project site(s) at times convenient to the parties concerned and will facilitate the discussion of the results and progress of the Project between the representatives of the Centre/MI and personnel responsible for the Project.

10. Return of Funds

Within a reasonable time after completion of the Project, JHU will return to the Centre/MI any grant funds not used for the Project.

11. Dissemination of Results

- a) JHU has the right to publish in any form the results of the Project, or any other information prepared or produced as a result of this grant, and is not required to obtain the consent of the Centre/MI to do so. JHU will recognize the support of the Centre/MI by including in all publications the following acknowledgement:

"This work was carried out with the aid of a grant from the Micronutrient Initiative, an International Secretariat of the International Development Research Centre, Ottawa, Canada."

Where appropriate, JHU will also secure an acknowledgement for the contribution of the Centre/MI in any reference made to the Project in speeches, press releases or similar publicity.

- b) The Centre/MI expects findings to the impact of maternal vitamin A and beta-carotene supplementation on pregnancy-related mortality to be published within a year of completion of the first trial, and the impact of maternal supplementation on infant mortality within a year of completion of field work for the second trial. Further, the Centre/MI expects no less than 3 papers addressing specific aims of each study to be published within three years of respective field work completion.
- c) JHU will provide the Centre/MI, in a timely manner, 25 reprints of each original publication and JHU agrees to provide the Centre/MI with reports of "work in progress" (eg. concerning manuscripts in preparation, under review, in press and published) on a periodic basis and on request by the Centre/MI throughout this 3-year time period, as assurance that the above schedule is being met.
- d) The Centre/MI may republish or represent findings from the Project, in accordance with international copyright regulations.
- e) The Centre/MI may request additional JiVitA analyses from JHU concerning specific issues of interest. JHU will evaluate and respond to such requests in a responsible and timely manner. Presentation of any unpublished findings provided under this subparagraph will require specific approval from JHU, with unpublished authorship credit lines and identification of all major funders of the study (USAID, Gates Foundation and the Centre/MI)
- f) Beyond specifications in Clause 12 c) and e), each party shall provide the other with five copies of any other publication it has made of the Project or of any other information prepare or produced as a result of this grant, and one copy of any audio or visual material.

12. Biomedical Research - Ethics

In accepting this grant, JHU agrees to comply with the International Guidelines for Biomedical Research Involving Human Subjects.

In particular, JHU agrees to comply with the following ethical principles which are aimed at protecting the dignity, the privacy and the integrity of every individual who, in the course of this Project, will be the subject of medical research or studies or will be requested to provide information about him/herself or others (hereinafter referred to as "a subject of research"):

- a) The research protocol for this Project has been reviewed in Bangladesh by an appropriately-constituted ethics review committee. Written confirmation of the committee's approval of the protocol shall be communicated to the Centre/MI as soon as possible.
- b) Notices and consents shall be given and obtained in accordance with the following:
 - i. Individuals will be provided with several notices throughout the course of the study, as set out in (ii) to (iv) below. Each such notice will be delivered from written text, either read or explained to the individual in simple and informative language. Each such notice will clearly identify the following:
 - . the aim, methods, anticipated benefits and potential hazards of the applicable research;
 - . the subject's right to abstain from participation in the research and the right to terminate participation at any time; and
 - . the confidential nature of replies given by the subject.
 - ii. A first notice will be provided by field workers while carrying out an initial census among women in rural Bangladesh. Women who agree verbally will be enrolled in the 5-week pregnancy surveillance phase of the research.
 - iii. A second notice will be given to any women enrolled as per (ii) above and who reports not having menstruated in the previous 5 weeks. Each such woman will be asked to consent to a pregnancy test, and will be informed of the test results, on a confidential basis.
 - iv. Any test positive woman will be visited by a trained interviewer, and will be asked to provide a separate consent, agreeing to routine supplementation, periodic interviews and limited anthropometry, as part of actual supplementation trials. The interviewer will be giving notice to each woman of the purpose, requirements, potential benefits and risk of participating in the supplementation trial. The interviewer will advise the subjects participating in the maternal vitamin A and beta-carotene supplementation trial (the first trial) as to their chances of receiving either vitamin A or beta-carotene verses neither of the

nutrients and in the second trial, subjects will be notified of their chances of receiving one of two planned micronutrient supplements verses neither. Interviewers will take care to explain to subjects that the process of random allocation among the three groups is not discriminatory and that if the outcome in one group is determined to be clearly superior to that in the others, the study will be terminated, so that all subjects may be offered the better treatment (see paragraph (h) below).

- v. Women participating in the study who are selected for an enriched sub-sample study will be asked to consent to blood sampling, both during pregnancy and postpartum, to be carried out in sterile conditions by qualified personnel.
- vi At 3 months post-partum, each woman participating in the enriched sub-sample study will be asked to provide a renewed consent, for blood sampling for both herself and her child (blood draw/heel stick, respectively), and for breast milk.
- c) No individual will become (or will continue as) a subject of research unless she is given the notices referred to in the preceding paragraph, and freely provides each of the consents required for participation or continued participation in the study. No pressure or inducement of any kind shall be applied to encourage an individual to become or remain a subject of research.
- d) The identity of individuals, from whom information is obtained in the course of this Project, shall be kept strictly confidential. No information revealing the identity of any individual shall be included in the final report or in any other communication prepared in the course of this Project, unless the individual concerned has consented in writing to this inclusion beforehand.
- e) JHU will take whatever steps may be necessary to ensure that effective treatment is provided to those subjects of research who react adversely to any aspect of the experimental procedure to which they have been subjected.

Any woman identified as severely ill at the time of enrollment (conclusion of the 5-week pregnancy surveillance), regardless of their participation in the study, will be offered a referral to the local health centre. Any woman who, at enrollment or in later interviews, reports symptoms for more than 2 out of the previous 7 days which relate to one or more serious illnesses, (e.g. lower abdominal pain, convulsions, swelling of hands or face, high fever, frequent watery stools, dysentery, blood in sputum, yellowing of eyes, painful/burning urination, excessive vaginal bleeding or discharge) will be

referred for treatment at a local treatment centre.

Any woman identified by researchers as pregnant at the time of enrollment, regardless of their participation in the study, will be provided with a pamphlet about pre-natal health, diet and care, which will include a list of conditions for which they should seek medical attention, including night blindness. It will be made clear to women participating in the study that participation in the study should not be viewed as substitute for sound ante-natal care.

Women tested for haemoglobin levels and found to be severely anaemic (Hb below 7g/dl) during pregnancy will be treated with iron-folate supplements, following WHO guidelines.

A sub-sample of women will be re-visited by trained interviewers during their third trimester: women then suffering from night blindness will be referred to the nearest health facility for treatment and follow-up.

While the study is in progress, local health care workers will be given periodic training on issues relating to malnutrition and disease prevention among pregnant women and children.

Children

- f) Because children will be involved in the Project, it is the policy of the Centre/MI that special care be taken to ensure that their participation is undertaken in accordance with high ethical standards. Accordingly, in addition to the requirements of paragraphs (a)-(e) being complied with, children shall not be allowed to participate unless:
 - i) their parents or guardians have been counselled with respect to the children's participation in accordance with the requirements of paragraphs (a)-(e); and,
 - ii) their parents or guardians have given their free, explicit and informed consent to the participation of the children in the Project.
- g) Parents or guardians shall have the right to withdraw their children from the Project at any time.

Mid-term assessment

- h) The Centre/MI subscribes to the ethical principle that where a procedure being tested is compared by the use of controls and is demonstrated to be clearly superior, the study should be terminated prematurely and the superior procedure should be promptly offered to members of the control group.

JHU therefore agrees that a mid-project assessment will be made to determine if sufficient evidence exists at that time to conclude that a significant benefit is being derived by a non-control group, and that the continued use of a control group is therefore no longer ethically justified. To this end, JHU will convene a mid-study data and safety monitoring committee (DSMC), comprised of independent experts, knowledgeable in reproductive health in developing countries and in the conduct and analysis of clinical trials, to review preliminary mortality data from the trial and to make appropriate recommendations to the investigators as to conduct and continuation of the trial, based on the strength of evidence on benefit and risk to participants.

JHU will report to the Centre/MI on the result of the mid-project assessment by the DSMC, for purpose of a review by the Centre/MI's Ethics Review Committee (ERC). Prior to that time, the Centre/MI's ERC will send a letter to JHU specifying the procedures it will enact to guarantee strict confidentiality of the Report, including the names of individuals who will have sole access to the report and where and how the report will be secured. The letter would also state that the Centre/MI will forward a copy of its own review report to the principal investigator at JHU. A copy of the Centre/MI's letter will also be placed on file with JHU's Committee on Human Research (CHR). JHU will request the Centre/MI 2 months before the mid term DSMC report to provide the above mentioned letter on confidentiality. Continuation of the project and disbursement of further project funds pursuant to this agreement will depend on the results of the assessment report. In the event that the report should disclose results which, in the opinion of the Centre/MI, preclude continuation of the trial for ethical reasons, the parties will consult on appropriate measures to be taken in addressing the needs of those who have up to that time been denied the benefits of the clearly superior procedure.

13. Ethical Compliance

JHU shall immediately report to the Centre/MI if it encounters any difficulties in complying with Clause 12 of this agreement. JHU shall indicate in the final technical report to be submitted to the Centre/MI, how it gave effect to the above-noted requirements in carrying out the Project.

14. Assignment of Contract

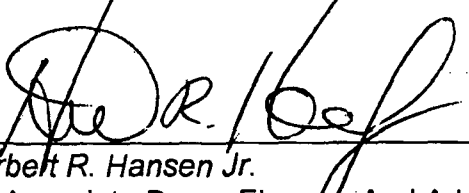
INF agrees that the Centre/MI may, as its option, assign all of its rights and responsibilities pursuant to this contract to any third party which succeeds or replaces the Centre as legally responsible for the affairs of the Micronutrient Initiative.

15. Project Leader

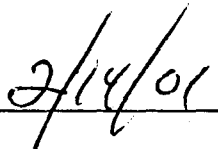
The Project will initially be led by Dr. Keith P. West, Jr., Professor, Centre for Human Nutrition, School of Public Health, Johns Hopkins University. The Centre/MI will be notified of any change in leadership occurring. It is condition of this grant that the project leader must demonstrate the required scientific and administrative skills to pursue successfully the objectives of the grant.

16. Availability of Grant

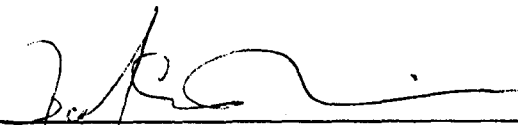
The estimated time for completion of the Project is 36 months from the date of acceptance by JHU of this grant. The Centre/MI grant will remain available to JHU during this period.



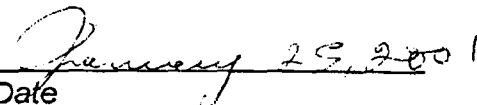
Herbert R. Hansen Jr.
Sr. Associate Dean, Finance And Administration
on behalf of the Johns Hopkins University



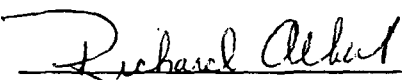
Date



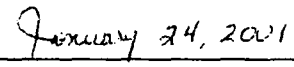
Raymond Robinson
Director, Finance and Administration
on behalf of the Micronutrient Initiative



Date



Richard Albert
Acting Coordinator, Client Services Group
on behalf of the International
Development Research Centre



Date

RA/ac

PROJECT: "JIVITA-Maternal Vitamin A and Micronutrient Supplementation Trial in Bangladesh"

<u>Budget</u>				
JHU Administered Funds (in American dollars)				
	<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Total</u>
Research Expense	<u>\$178,500</u>	<u>\$178,500</u>	<u>\$63,000</u>	<u>\$420,000</u>
TOTAL FUNDS ADMINISTERED BY JHU (in American dollars)	<u>\$178,500</u>	<u>\$178,500</u>	<u>\$63,000</u>	<u>\$420,000</u>
TOTAL FUNDS ADMINISTERED BY JHU (in Canadian dollars)	<u>\$274,890</u>	<u>\$274,890</u>	<u>\$97,020</u>	<u>\$646,800</u>

The above budget has been based on a current exchange rate of \$1.00 American dollars (USD) equals approximately \$1.54 Canadian dollars (CAD). The Centre/MI's liability is limited to the amounts quoted in Canadian currency.

IF YOU ARE LOCATED OUTSIDE CANADA
PLEASE COMPLETE THIS FORM AND RETURN
WITH THE SIGNED MGC

* ***Incomplete information will delay your payment.*** All banking information can be obtained from your bank. Please notify us of any changes in the above during the course of your contract.

Bank name	
Bank street address or branch name (no P.O. Box)	
City, country	
Swift code	
Account number	

THIS FORM MUST REMAIN ATTACHED TO THE MGC.