# INTERNAL USE ONLY

# First Look: A Cluster-Randomized Trial of

# Ultrasound use to improve pregnancy outcomes in low income country settings

NICHD Global Network for Women's and Children's Health Research

*with support from*

The Bill & Melinda Gates Foundation and GE Healthcare

*and participation by*

Faculty from the University of Washington

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## Executive Summary

With focused investment and sustained action, global maternal mortality declined 35% from 1980 to 2008 and newborn mortality declined 24% from 1990 to 2010. Despite these noteworthy gains, achieving United Nations Millennium Development Goals (MDGs) 4 and 5 to reduce maternal and child mortality by 2015 will necessitate investment in proven interventions and concurrent investigation of new interventions. Obstetric ultrasound is part of current care in high-resource settings and a tool used to identify complications of pregnancy as well as to establish accurate gestational age. With reduced costs of ultrasound technology as well as increased durability, ultrasound is increasingly being disseminated in low-resource settings but its impact on maternal and newborn mortality in these settings has not been assessed. With limited resources for health care in low-income countries, identifying low-cost, effective strategies to reduce maternal and newborn mortality is needed.

The use of compact ultrasound by physician and non-physician health care staff for antenatal identification of high risk pregnancies is a potentially effective intervention; however, authoritative investigation in many low-resource settings is needed to establish its potential impact. We propose to undertake a multi-country cluster randomized trial to assess the impact of antenatal ultrasound screening performed by community physician and non-physician health care staff on a composite outcome consisting of maternal mortality and near miss maternal mortality, stillbirth and neonatal mortality in low-resource community settings. Underpinning this objective are several assumptions. The first assumption is that ultrasound's introduction will increase antenatal attendance and improved outcomes due to the antenatal care alone, and greater rates of institutional delivery. The second assumption is that ultrasound use will lead to antenatal detection of complicated pregnancies and timely and appropriate referral for complicated pregnancies to comprehensive emergency obstetric and neonatal care (EmONC) facilities. Increases in antenatal care utilization and referral will result in a decrease in a composite outcome including maternal mortality and near miss mortality, stillbirth and neonatal death. Secondary outcomes to be evaluated include antenatal attendance rates, institutional delivery rates at basic EmONC facilities, referral rates to comprehensive EmONC facilities, cesarean section rates (both planned and emergent), an assessment of community physician and non-physician health care provider ultrasound training and competence and the cost-effectiveness of ultrasound in community health facilities. We will also determine causes for non-compliance with recommendations for referral. The costs, consequences, and overall expected benefit of these measures to the health system will be evaluated.

**In summary, our study will evaluate whether training ultrasound-naïve providers to perform basic obstetric ultrasonography and using these trainees to provide routine ultrasounds in primary care clinics and to refer appropriately improves pregnancy outcomes in low-resource settings.**

To assess the impact of ultrasound, we propose to utilize an existing research infrastructure, the Global Network for Women's and Children's Health Research (Global Network), which currently includes 6 sites in 5 countries, India (2), Pakistan, Kenya, Zambia, and Guatemala. The investigators of the Global Network have an ongoing maternal and newborn health registry to document all pregnancies and their

outcomes to 6 weeks post-delivery in 110 communities. Thus, population-based rates of maternal mortality and morbidity, stillbirth, and neonatal mortality and morbidity, as well as health care utilization, are being obtained. Furthermore, the Global Network has an excellent record of being able to efficiently implement large, cluster-randomized trials in these settings. RTI International serves as the data coordinating center for the Global Network to help facilitate the design and conduct of the trial, manage the trial related data, and provide statistical analyses of the trial results. GE Healthcare will provide the ultrasound equipment, and will also fund the University of Washington to provide training and technical support on the implementation of ultrasound in community settings. Together, the Global Network with the support of the University of Washington and GE Healthcare will maximize the resources necessary to conduct the definitive trial on the potential impact of ultrasound to reduce maternal and newborn mortality and maternal morbidity in low-resource settings.

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## Abstract

With focused investment and sustained action, global maternal mortality declined 35% from 1980 to 2008 and newborn mortality declined 24% from 1990 to 2010 (Hogan, Rajaratnam, 2010). Despite these noteworthy gains, achieving United Nations Millennium Development Goals (MDGs) 4 and 5 to reduce maternal and child mortality by 2015 will necessitate investment in proven interventions and concurrent investigation of new interventions. The use of compact ultrasound by medical officers and non-physician health care staff (e.g., midwives) for antenatal identification of high risk pregnancies is a new intervention requiring authoritative investigation in many low-resource settings. The primary hypothesis to be assessed in this study is that antenatal ultrasound screenings performed by medical officers and non-physician health care staff will significantly reduce a composite outcome consisting of maternal mortality and near miss maternal mortality, stillbirth and neonatal mortality in low-resource settings. Underpinning this hypothesis are two assumptions. The first assumption is that antenatal detection of complicated pregnancies will lead to appropriate referral at the right time for complicated pregnancies to comprehensive emergency obstetric and neonatal care (EmONC) facilities. The second assumption is that ultrasound's introduction will increase antenatal attendance leading to greater rates of institutional delivery. To assess these underlying assumptions beyond the composite end point, this study will investigate the health system impact of compact ultrasound. Secondary outcomes include antenatal attendance rates, institutional delivery rates at basic EmONC facilities, referral rates to comprehensive EmONC facilities, cesarean section rates (both planned and emergent) and an assessment of medical officers and non-physician health care provider ultrasound competence and training quality. The expected costs and consequences of these measures and the impact of compact ultrasound on the health system will be estimated.

# 1. Background and Significance

Maternal, fetal and neonatal mortality are 10 to 100 fold higher in many low-income compared to high-income countries. The reasons for these discrepancies are many, but include the facts that many women and newborns receive little prenatal care and most deliver outside of facilities that can provide lifesaving treatment for the mother, fetus and newborn. While many interventions have been studied, there is growing interest in and existing controversy regarding the potential impact of obstetric ultrasound on maternal, fetal and newborn survival in developing countries.

In low-income settings, maternal mortality rates range from 150 to more than 1000 per 100,000 live births (Khan, 2007) while rates of stillbirth and neonatal mortality generally range from 20 to 40 per 1000 births (McClure 2011; Oestergaard 2011). Intrapartum stillbirth, or those stillbirths that occur during labor and delivery, are an important indicator of the quality of obstetric care (Goldenberg 2008; McClure 2007). While in high-income countries, intrapartum stillbirths have nearly been eliminated, in low-resource settings up to half of all stillbirths occur in the intrapartum period. Another measure of obstetric care is obstetric 'near miss' which has been defined by the World Health Organization (WHO) to comprise women who nearly died but survived a complication during pregnancy (Say 2009; Pattinson 2011). Near misses are considered an important indicator of maternal mortality and rates may be as high as 33 per 1000 in low-resource settings (Okong 2007; Mustafa 2011; Ali 2009; Almerie 2010). Because maternal mortality is relatively rare and therefore difficult to study, many have advocated using near miss cases as a surrogate measure of maternal mortality, although the morbidity is an important outcome in its own right.

It is widely accepted that 15% of all pregnancies have medical or obstetric complications that greatly increase the risk of mortality or severe morbidity for the mother and newborn (Maine, 1991). Universal access to high quality facility care substantially reduces mortality and morbidity from these conditions (e.g., Yakoob 2011). Poor quality and reduced access to antenatal care result in failure to detect and potentially refer these high risk pregnancies in low- and middle-income countries. In high-income countries, access to prenatal care is nearly universal. As part of that care, in most high-income countries, obstetric ultrasound is used routinely in the antenatal period for determining gestational age and screening for potential complications including multiple gestations, fetal anomalies, mal-presentation, placenta previa, and others. In low-income countries, factors including cost of the ultrasound and high skill level required to operate the equipment have been among the barriers to adopting it widely.

The inequality in pregnancy outcomes, the global push to accelerate fulfillment of the UN Millennium Development Goals (MDGs) 4 and 5 to reduce maternal and child mortality, and reductions in the size and cost of electronics have all increased interest in the use of ultrasound to improve pregnancy outcomes in low- and middle-income countries. Increased interest, however, does not imply consensus on ultrasound's ability to improve maternal and newborn health. Views on obstetric ultrasound vary from region to region and diverge considerably across sectors. Public health academicians often cite a Cochrane review that summarized studies conducted in high-resource settings that concluded that routine late ultrasound (after 24 weeks) had no measurable benefit for mother or baby (Bricker, 2008).

In part due to the greater potential for outcome improvement, practicing obstetricians and gynecologists often tout the merits of obstetric ultrasound performed by midwives in low-resource settings but lack objective verification of any benefit (Harris, 2009). Ministry of Health officials in low- and middle-income countries have considered compact ultrasound to be an attractive tool to increase appropriate delivery in EmONC facilities, but lack the clinical and economic evidence of net benefit to secure multi- or bi-lateral funding. Manufacturing companies are keen to grow the compact ultrasound market and solve unmet needs to help achieve MDG 4 and MDG 5 goals, but remain averse to investing without cross-sector alignment. Given the lack of consensus and supportive evidence on the value of ultrasound in improving outcomes by earlier, antenatal detection of complicated pregnancies, an authoritative investigation on ultrasound's utility in low-resource settings, which has never been undertaken, will be important and timely.

Figure 1. Kenya Global Network Clusters

## 1.1 Previous and Ongoing Studies of the Global Network/Potential Conflicts

This cluster randomized controlled trial( RCT) will be undertaken in the sites of the Global Network for Women's and Children's Health Research Network (Global Network), which is funded by NIH and includes sites in Democratic Republic of Congo (DRC), Kenya, Zambia, Pakistan, and Guatemala, with RTI serving as the data coordinating center. Founded in 2001, the Global Network conducts multi-country research to improve maternal, fetal and newborn outcomes in low-resource settings. The Global Network has conducted a number of single site studies, including misoprostol to reduce post-partum hemorrhage in India and a maternal/neonatal wash with chlorhexidine to reduce maternal and newborn sepsis in Pakistan. Multi-site cluster randomized trials include FIRST BREATH, a trial of newborn resuscitation training for community health workers, a study focusing on community mobilization to improve pregnancy outcomes, and a current study on the community use of antenatal corticosteroids (ACT) to reduce preterm mortality associated with newborn respiratory distress syndrome and a study of neonatal resuscitation. (Currently, ACT is the only ongoing trial in all Global Network sites; it will be completed in 2013, before the primary data collection for the ultrasound study is underway. Additionally, since the target of antenatal corticosteroids is preterm infants, it will not likely have an important impact on the overall outcome, since most stillbirths and neonatal deaths in the Global Network are term infants. It should have no impact on maternal deaths or near misses. Furthermore, since the clusters will be randomized for the ultrasound study, there will be a similar number of ACT intervention clusters in both the ultrasound control and intervention clusters.)

In 2008, the Global Network initiated the Maternal-Newborn Health Registry (MNH Registry), a prospective study in which pregnant women are enrolled and followed to 42-day post-partum in study clusters and in which virtually all pregnancy outcomes in the current clusters are ascertained. Each pregnant woman is enrolled during her pregnancy in the Registry by a Global Network MNH registry administrator, with informed consent provided by 98% of pregnant women.

Currently, MNH Registry clusters within the Global Network are defined by having a specific geographic boundary with from 300 to nearly 1,000 deliveries per year (Goudar, 2012). The clusters are rural and generally have a number of villages and generally one health center, but some have several. Several clusters may use one referral hospital (Figure 1, Kenya as an example). There are currently 110 clusters in the Global Network sites. While it is our intent to use many of the existing clusters, we will need to redefine several to ensure that they are more balanced in terms of number of deliveries and that each has one central health clinic. We have initiated a mapping exercise in each of our sites to evaluate the location of the individual clinics, the location of the referral hospitals, and the boundaries of each governmentally defined political unit. We will use this information to redefine any cluster that does not conform to the ultrasound project specifications. Since we are aware that in most of the sites, a number of clusters refer to one district hospital, we do not believe it is possible to direct intervention cluster women to one hospital and control cluster women to another hospital. This situation should not harm project conclusions, since we are testing whether the introduction of routine ultrasound testing into the intervention clinics improves outcomes. We will be able to follow trends in our outcomes over time in each cluster to know whether the control clusters improved their outcomes over time. We will also be able to track the percentage of women in the control compared to those in the intervention clusters who were referred to and received care in hospitals.

## 1.2 Studies of Ultrasound and Pregnancy Outcomes in Low Income Settings

A literature review on obstetric ultrasound use by paraprofessionals in low-resource settings has been conducted. The majority of studies of antenatal ultrasound in low-resource settings conducted to date were not powered to identify meaningful trends in maternal and newborn outcomes. Clinical competence of paraprofessionals (midwives, paramedics, etc.) in obstetric ultrasound has been proven and replicated by several studies. There is also promising evidence that basic obstetric ultrasound training can be successfully achieved with paraprofessionals in a 2-3 week time frame. A number of studies acknowledge the positive psychological benefit for mothers through the introduction of obstetric ultrasound that has been associated with increased facility utilization. In addition to the above summary of key findings and the literature review, PATH has also reported on the paucity of data on ultrasound and maternal mortality.(Tsu, 2009) Based on this literature review, we have listed some potential pregnancy-related benefits and risks to the use of ultrasound in developing country settings (Tables 1, 2).

**Table 1. Conditions That Could Potentially Be Diagnosed by Ultrasound**

- Gestational age used for diagnosing prematurity and post-dates
- Placenta previa
- Fetal malposition
- Multiple gestations
- Ectopic pregnancy
- Retained placental products following delivery
- Fetal anomalies

- Fetal growth restriction
- Short cervix (increased risk of preterm birth)
- Poly- and oligio-hydramnios
- Fetal demise
- Obstructive fibroids

**Table 2. Potential Benefits Related to Ultrasound Use**

Specific benefits related to health care:

- Increased enrollment in prenatal care (access to testing for syphilis, iron/vitamins, etc.)
- Increased basic facility usage for delivery for women with uncomplicated pregnancies
- Increased hospital referral for delivery for women with complicated pregnancies
- Decreased inappropriate transfers
- Recruitment and retention of community physicians and midwives
- Specific diagnostic information to inform expecting mothers to deliver in a risk-appropriate setting

Potential outcomes achieved with widespread prenatal ultrasound:

- Reduction of maternal mortality and maternal near-miss morbidity
- Reduction of fetal and newborn mortality
- Rational management of preeclampsia/eclampsia, fetal growth restriction and other conditions related to gestational age dating
- The ability to treat women with a short cervix with progesterone or a pessary to decrease preterm birth
- Appropriate treatment of women with incomplete abortion, ectopic pregnancy, and fetal demise
- Reduction in emergency care for birthing complications due to more deliveries in risk-appropriate settings

In addition to the potential benefits, there are also a number of potential challenges and issues associated with introducing ultrasound in low-resource settings (Table 3). Together, the issues reviewed (Tables 1-3) suggest the need for a multi-country trial to evaluate the potential for ultrasound to improve maternal and perinatal outcomes in low-resource settings.

**Table 3 Challenges and Issues Related to Introduction of Ultrasound in Low-Resource Settings**

*Potential challenges with the introduction of ultrasound include:*

- Security of the ultrasound machine
- Prevention of the use of the ultrasound equipment for sex determination/selection
- Infrastructure requirements, including electricity and maintenance

- Training issues for community physicians and para-professionals
- Diversion of resources from other clinical activities to ultrasound
- Use of resources required for life saving interventions to expenditures for US equipment
- Increase in unnecessary interventions
- Attrition of trained ultrasound personnel
- Health facilities improving to meet increases in demand generated by ultrasound
- Sustaining funding for continuous improvement in ultrasound training and care delivery

*Issues related to training various providers to use ultrasound identified include:*

- Defining the level of health care personnel who can be effectively trained in ultrasound use.
- Country regulations for type of health professional allowed to be certified in ultrasound use.
- Acceptability at the policy level of this trial to train health care professionals other than physicians and sonographers.
- Defining the type and length of training required to achieve reliable diagnoses by community physicians and non-physicians with various levels of training.
- Determining how well ultrasound can identify various conditions at different levels of care.
- Logistics of providing care while essential personnel are in ultrasound training.

Furthermore in the State of Alabama from 1976 to 1981 the provision of ultrasound machines to mostly rural hospitals was done aimed at increasing hospital deliveries for women who otherwise would have delivered at home. From 1976 to 1979, Alabama's infant mortality was reduced by nearly half, in large part due to a reduction in neonatal mortality associated with hospital delivery (Robert Goldenberg, personal communication).

## 1.3 Specific Aims

**Our primary aim is to evaluate whether training ultrasound-naïve providers to perform basic obstetric ultrasonography and using these trainees to provide routine ultrasounds in primary care clinics and to refer appropriately improves pregnancy outcomes in low-resource settings.**

The specific aims include the following:

### 1.3.1 Primary aims:

- To evaluate whether use of ultrasound in community health centers increases antenatal care attendance.
- To evaluate whether use of ultrasound in community health centers increases the utilization of delivery facilities for women with pregnancy complications.
- To evaluate whether ultrasound use in community health centers reduces a composite outcome of maternal mortality and near miss mortality, stillbirth, and neonatal mortality.

### 1.3.2 Secondary aims:

*Specific Aims, Training*

1. Assess and improve the effectiveness of the two-week ultrasound training program for midwives by:

   - analyzing quantitative data (written and scanning skills tests), and
   - analyzing qualitative data (observer's guide, daily feedback questionnaire, and final evaluation)

2. Assess the adequacy of screening ultrasound in the field by performing ongoing quality assurance activities.

## 1.4 Hypotheses

We will conduct a multi-country cluster RCT to test two hypotheses.

The first hypothesis (with two components to be assessed individually) is that ultrasound will 1) increase the rate of prenatal care utilization and 2) will increase utilization of delivery facilities for women with complicated pregnancies.

The second hypothesis is that antenatal ultrasound screening performed by community physicians and non-physician health care staff will improve a composite outcome of maternal mortality, maternal near miss mortality and stillbirth and neonatal mortality. Specifically, we hypothesize that introduction of ultrasound will decrease the composite outcome (including maternal mortality and near miss maternal mortality events and stillbirths plus early neonatal mortality.

These two hypotheses will be tested independently without controlling for multiplicity.

Additional secondary outcomes include the difference between ultrasound and non-ultrasound clusters in rates of maternal mortality, maternal morbidity, neonatal deaths, intra-uterine growth restriction-related mortality, and intrapartum stillbirths. The sample size determination will be based on a potential reduction in the composite outcome between the control and intervention clusters of 20%.

Because the effectiveness of training is an important consideration in implementing its use, one additional component of the project will be evaluation of the training component conducted by the faculty at the University of Washington working under the direction of the Global Network Steering Committee. Given that the costs and consequences of implementing ultrasound interventions are important considerations, we also plan to perform cost evaluation of the ultrasound use (we are currently seeking funds for this analysis). Data necessary for this evaluation will be collected as part of the overall project data base and will be analyzed by project investigators including those from the University of Washington under the direction of the project steering committee.

## 1.5 Study Design

### 1.5.1 Overview

The study design will be a cluster RCT with intervention and control clusters stratified by study site (country), while also considering factors such as historic perinatal mortality rates and logistic factors

such as travel time to comprehensive EmONC facilities. Each ultrasound cluster will be defined by a health center and its catchment area. The clusters will be randomized to the intervention group or to the control group. The main study intervention will be to offer routine ultrasound examinations to all intervention cluster pregnant women in order to encourage utilization of prenatal care, to identify pregnancies with complications among women in low-resource, usually rural, settings and for pregnancies identified with complications to offer appropriate referral to a higher level of care. For the intervention clusters, while flexible, the general plan is to develop an ultrasound team consisting of one to two ultrasonographers and an assistant who will serve approximately 5 health clinics (or clusters), spending 1 day per week at each clinic so it will be known that, on a given day of the week, prenatal ultrasound will be available at a specific clinic. The field team of ultrasonographers and an assistant will be overseen by a project sonographer at the referral hospital associated with the intervention cluster. Therefore if a study site has 20 clusters, there will generally be 2 teams of ultrasound providers together serving 10 intervention clusters. An additional 10 control clusters will collect outcome data but will not have active intervention activities.

With specific regard to Kenya, there will be an ultrasound per health clinic for purposes of compliance to the study and Ministry of health requirement that there should be a fixed intervention per cluster. As in all the sites, the ultrasound machines will be kept in a safe locked area and use will be restricted to project personnel.

The project goal is to provide two routine prenatal ultrasound examinations to each pregnant woman living in the ultrasound intervention clusters. (We emphasize that we are studying the impact of routine ultrasounds—not emergency ultrasounds—but will provide emergency ultrasounds in the clinics and hospitals if the project sonographer and equipment are available.) The first ultrasound will generally be done around 18-22 weeks gestational age to document the number of fetuses, gestational age, amniotic fluid abnormalities, major congenital anomalies, and possibly cervical length. (To schedule this ultrasound, we will use the LMP-based estimate of gestational age and if not available, we will use fundal height measurement to estimate gestational age and perform the ultrasound exam when the fundal height measures about 20 cm.) A second ultrasound examination will be offered at 32 - 36 weeks to document placenta location, growth abnormalities, amniotic fluid abnormalities, and fetal malposition. (The timing of this ultrasound will be based on the GA determined by the first ultrasound.) In addition to the two routine study examinations, clinically indicated examinations may be performed, but, as stated above, only if the ultrasound machine is on site with available project sonographers at the time of the patient's appearance. If the ultrasound appears to be indicated and the test is not available, the patient will be referred to the hospital for care and further testing. Symptoms that could prompt a clinical ultrasound include abdominal pain prior to delivery, abnormal bleeding prior to delivery (previa, abruption), bleeding related to a miscarriage, ectopic pregnancy or abortion, intrauterine growth restriction (IUGR), or post-partum bleeding (retained products). Based on the results of any of these ultrasound examinations, mothers will be counseled about the need to seek care or deliver at a referral hospital. Because we believe that providing a picture of the ultrasound exam will increase clinic utilization, each of the ultrasound machines will be provided with a printer so that pictures of the fetus could be provided to the mother at each visit.

We have considered the feasibility of providing adequate ultrasound coverage to all pregnant women in a cluster on a one day a week schedule. If in a typical cluster there are 500 deliveries per year, because each woman will have 2 ultrasound examinations, this means that there will be a maximum of approximately 1,000 exams per year per cluster if every woman is tested twice. With 50 testing days (one testing day per cluster per week) this means there will be a maximum of 20 exams per day, and most likely less, (estimated at 10 to 15 exams per day), well within the capability of a single sonographer. (In specific countries or settings, to make the cost of the testing more affordable, it may be necessary to share the costs of the equipment and staff among several clinics. Thus we plan to use sensitivity analyses to estimate costs associated with single-site models and multiple clinic models when we assess costs and consequences.

### 1.5.2 Global Network Maternal and Newborn Health (MNH) Registry

The ultrasound trial will use the Global Network MNH Registry, and within each of the ultrasound study clusters, every pregnancy will be counted and the outcome determined. While there may be a referral hospital within the geographic boundaries of a cluster, typically several clusters/clinics will refer obstetric emergencies to one EmONC hospital. Thus any given hospital will usually draw its patients from a number of clusters. We emphasize that we are testing the provision of routine ultrasounds in clinics. The ultrasound clusters will provide this intervention, while the control clinics will not. While having an ultrasound machine in the referral hospital may benefit women from both the intervention and control clusters, we are not testing that in this trial. However, because we will have historical registry data, we will be able to assess whether there were improvements in the outcome measure in both types of clusters over time.

In the ultrasound study control clusters, no ultrasound machines will be provided to the clinics, there will be no community notification, and there will be no attempt to provide additional training to clinic staff. Data on pregnancy outcomes will be collected in a similar fashion in both the ultrasound control and the ultrasound intervention clusters by Global Network MNH Registry personnel. Since the referral hospitals that serve the ultrasound intervention clusters will not be randomized and may draw women from the US intervention and ultrasound control clusters, some women from ultrasound control clusters may deliver at these EmONC hospitals. These women and their newborns will of course have the benefit of the training received by the medical staff at those hospitals, and as medically necessary, would not be denied ultrasound services at the referral hospitals. Since each current cluster has historical data, including rates of pregnancy outcomes, hospital use, receipt of prenatal care, and transports, which will be able to be ascribed to the ultrasound clusters derived from the same geographic areas, we will be able to use the historical data to verify the validity and generalizability of the cluster randomized trial results. We realize that the availability of ultrasound may cause women from control clusters to seek care at intervention cluster clinics. However, most of our clusters are in rural areas, often with poor transportation between their clinics. Expending significant effort to seek care in a distant clinic will likely not occur very often. However, if it does occur, since we track the residence of each pregnant woman residing in all the clusters, we will be able to monitor this movement, if it occurs, and try to discourage it. However, which women will be provided antenatal care in the individual clinics will be a local decision.

### 1.5.3 Study Inclusion/Exclusion Criteria

A study cluster defined as health center and its catchment area and meets the following criteria >

Inclusion Criteria:

- A health center that provides prenatal care and its catchment area with 300-500 births/yr (minimum of 500 births in 18 months)
- Referral facility available within 4 hours of health center

Exclusion Criteria

- Current use of routine ultrasound at the health center for antenatal care at time of study initiation

All pregnant women who present at a study clinic for antenatal care should be screened for the study. The following are the inclusion and exclusion criteria

Inclusion criteria:

- Women who provide consent
- Resident of study cluster (reside in area for at least 4 weeks, see study manual for details)
- Enrolled (or eligible) in the Global Network MNH study
- Women ≥ 18 weeks gestation at the antenatal care visit

Exclusion criteria:

- Women who are in labor at time of antenatal care
- Women who are < 14 years of age

### 1.5.4 Study Pilot

As part of the study, we will include a 3 month pilot period following the initial sonography training (described below) to ensure that the study procedures have been implemented. Specifically, the following will be evaluated in the study pilot period:

1. The effectiveness of the training to train project sonographers to obtain adequate exams.
2. The integration of the ultrasound team into the prenatal care plan at the clinic
3. The number of ultrasound exams possible in a given time period in each setting
4. The effectiveness of the referral system for complication
5. The ability of the referral hospitals to care for those referred
6. The ability of the registry staff to collect data at the referral hospitals
7. The ability of the ultrasound team to collect and record accurate data
8. The ability of the entire team to provide quality assurance for the ultrasound exams

## 1.6 Other Study Issues

While it is clear that the major intent of the project is to study the effect of ultrasound on improving pregnancy outcomes and appropriate referral, it is also clear that an ultrasound machine cannot be placed in a clinic and achieve benefit without health workers who have appropriate training and backup for questions, continued quality assessment, and oversight. Therefore, an important component of the study will entail training of the health workers in the use of ultrasound, and the conditions that require referral. It is also important that pregnant women and the community at large be aware of ultrasound availability. Thus, it is also clear that the project will require a community notification and sensitization component in order to increase awareness of ultrasound and complications of pregnancy. This process will be directed not only at the pregnant women, but at the husbands and family, and community leaders. Since this is primarily a trial to evaluate ultrasound use rather than community mobilization, we have elected to limit our community involvement to notification about ultrasound availability and its potential benefits during pregnancy, but will try to answer all questions that arise from the community about ultrasound during the trial. We also plan to have sufficient staff available at each ultrasound exam to explain all findings to the patient and her family, and facilitate referrals for confirmatory ultrasound and additional counseling, as needed. We have designed community notification ultrasound fact sheet that will be made available in the local language and distributed widely. Similar information will be included in posters visible to the public at the health centers.

Having a referral institution with staff trained to review and confirm ultrasound findings and manage complications referred to it and the resources to provide care for those complications is crucial. An important question, therefore, is whether the referral facility has the capacity and willingness to provide increasing quantities of care, and that the care provided is timely and of reasonable quality. At a minimum, we believe that the successful introduction of ultrasound into primary health centers and clinics will require a thorough evaluation of the health systems' capabilities, and discussion with local policy makers and providers to ensure that each participant's issues regarding the project are considered, with specific care being taken not to overwhelm fragile hospitals with more patients than they can effectively manage. In particular, we will work with the referral hospitals regarding management of referrals in order to enhance the referral system. This is important, since there is little benefit of hospital referral unless the hospital can appropriately manage the obstetric complications referred to it. Thus, we feel it is important to assess each hospital's capacity to provide care and to work with each hospital and the health system to improve specific weaknesses discovered during the assessment. Providing some facility training, resources to upgrade care and a hospital-based ultrasound machine are ways to increase buy-in by the local hospitals. Therefore, we include in this project, training of hospital staff in the appropriate care of obstetric complications including preeclampsia/eclampsia, abruption, and in the performance of inductions of labor, cesarean sections and new born resuscitations. The project will identify a sonographer at the referral hospital(s) who will be provided with additional training, participate in the review of referred ultrasounds and communicate with the study sonographers. We will also seek to obtain input and support of country and local OBGYN societies and radiologists. (If resources are needed for the facility to provide EmONC care, we will work with the health system to provide those resources. We will use project funds for essential medications and equipment only as a last resort.)

## 1.7 Training

There will be two primary training components for this trial.

### *1) Obstetric Sonography Training*

The first component will be in training of the community midwives, physicians (medical officers), other health workers, and hospital OBGYN physicians in ultrasound use, diagnosis, and appropriate referral. For each site, the cadre of trainees may vary (e.g., medical officers, nurse midwives or physicians, but the objective is to have a community health provider available at the health center to provide routine ultrasound for antenatal care). Additional training will be provided to the relevant staff at the primary referral facility to ensure the continuity of health care provision. This ultrasound training will occur under the direction of Dr. Robert Nathan, a radiologist based at the University of Washington. With oversight by the Study Management Committee (see Figure 2, Section 3.2), the University of Washington will develop the curriculum of the ultrasound training, evaluate the skills of each trainee, and certify trainees who successfully complete the course to participate in the study. This team will also train a local QC sonographer located at the referral hospital to oversee and provide ongoing training, quality assurance, and evaluation of each trainee. Data collected from this component of the trial will be used to evaluate trainee competence, provide oversight, and to determine ongoing training needs of those instructed in obstetric ultrasound.

For the training, UW will utilize the Basic Obstetric Ultrasound Training Instructor Guide and Basic Obstetric Ultrasound Participant Manual (Appendix1) authored by UW Radiology.

The course will include pre-post written tests and a scanning skills test at the completion of class. Additionally, trainees will also complete a final evaluation at the end of the course.

Quantitative and qualitative data will be analyzed to assess the strengths and weaknesses of the course. Attention will be directed to test results, participant involvement, use of teaching materials, and flow of the content. As a result of this analysis changes may be made to the length or content of lectures or hands-on sessions, or methods of instruction. These changes will be incorporated into subsequent courses.

UW will work with each of the Global Network sites to help tailor QA systems to the varying situations each site is likely to present. Depending on the site, clusters may have their own ultrasound machines or may be served by a traveling sonographer. These systems will include a means of storing images of the field sonographer scanning and of having these images reviewed by the referral hospital sonographers, referral hospital obstetricians, and UW, to varying extents. All scans identified by the field sonographer indicating a complicated pregnancy (multiple gestation, mal-presentation, placenta previa, ectopic pregnancy, blighted ovum, miscarriage, fetal anomaly) will be sent to the referral hospital for a confirmatory scan by the referral sonographer (features of the program are shown in Table 4). All scans performed at the intervention clusters in the first three months post training will be reviewed and scored for accuracy. Sensitivity and specificity of field sonographer ultrasound will be tabulated for each sonographer with sensitivity defined as the number of correctly diagnosed pregnancy complication as determined by the field sonographer divided by the total number of diagnosable complications as

determined by the confirmatory review scan. Specificity will be defined by the number of cases without a complication correctly called as complication free by the field sonographer by all cases without a complication as determined by review. Each field sonographer error will be recorded.

UW in conjunction with the referral hospital obstetrician or radiologist will review the field sonographer ultrasound results weekly during the first three months post training. Field sonographers will be informed of all errors, and remedial training will be undertaken by the referral sonographers as deemed necessary. If the accuracy threshold (sensitivity .70, specificity .97) is not reached after the first three months for an ultrasound unit all scans will be reviewed for that unit for an additional three months. If the accuracy threshold is reached for an ultrasound unit, a random sampling of 20% of scans will be performed subsequently.

The QA data will be reviewed for systematic errors in scanning. These errors will be addressed not only remedial training to field sonographers but also by making adjustments to subsequent courses.

**Table 4. Ultrasound Training Program (Example)**

| DAY # | LECTURE | HANDS-ON CLINICAL |
|---|---|---|
| 1 | • Introduction<br>• Physics and Knobology<br>• Tomography | • Introduction to the Equipment<br>• Transducer Orientation and Tomography<br>• Interpreting Structures |
| 2 | • Infection Prevention & Control<br>• 2nd Trimester Anatomy<br>• 2nd Trimester Biometry | • The Patient<br>• Preparing to Scan<br>• ROBUST Technique |
| 3 | • Normal Pelvis<br>• 1st Trimester Anatomy<br>• 1st Trimester Biometry | • Non-pregnant Pelvis<br>• Biometry<br>• Biometry |
| 4 | • Amniotic Fluid<br>• Placenta | • Amniotic Fluid<br>• Placenta<br>• The Cervix<br>• ROBUST and Biometry Practice 1 |
| 5 | • Fetal Position<br>• Multiple Pregnancy | • ROBUST and Biometry Practice 2<br>• Fluid, Placenta and Cervix<br>• Introduction to 2nd/3rd Trimester Screening Ultrasound<br>• Screening 2nd/3rd Trimester Ultrasound |
| 6 | • Review Week 1<br>• 1st Trimester Bleeding (1) | • Screening 1st Trimester Ultrasound<br>• Screening Ultrasound Practice |

| | | |
|---|---|---|
| 7 | • 1st Trimester Bleeding (2)<br>• Ectopic Pregnancy | • Screening Ultrasound Practice |
| 8 | • IUGR<br>• Anomalies | • Biophysical Profile<br>• Screening Ultrasound Practice |
| 9 | • Case Studies (1-2) | • Screening Ultrasound Practice |
| 10 | • Case Studies (3-5) | • Practical Testing |

## Didactic modules

Local training coordinators will arrange for pregnant volunteers in the first, second, and third trimesters as well as non-pregnant volunteers to serve as subjects for hands-on scanning.

If not contrary to local policy, trainees will observe scanning or will be allowed to scan patients with fetal anomalies, ectopic pregnancy, incomplete abortion, fetal demise, molar pregnancy, fibroids, or other abnormal conditions.

*Note:* As part of the training, strong attention will be given to a prohibition about using ultrasound for fetal sex identification (using a protocol developed for this training). The ultrasound machines have capability to download images and will be reviewed periodically to ensure that the machine is not used for sex identification. All sonographers will be made aware of this capability.

We emphasize that the issue of using the ultrasound machine for fetal sex determination has been discussed extensively among the investigators, with GE Healthcare, and with representatives of the University of Washington. We have universal agreement that in this study fetal sex determination will not be performed. The training will strongly emphasize that fetal sex determination is not to be performed. GE Healthcare has confirmed that every ultrasound exam performed will be recorded and can be evaluated to determine whether the sonographer is performing scans for fetal sex selection. The ultrasound machines will be secured in the clinics so that they cannot be used for non-study purposes. We will emphasize that any project sonographer caught doing fetal sex determination will lose his/her job immediately. Also, we will require two staff members to be present for each exam to help ensure that sex determinations do not occur.

It is essential that the trained community ultrasonographers perform screening ultrasound correctly and that they accurately report results at all sites. Ultrasound quality assurance (QA) will be ongoing throughout the trial and include the following activities:

- Adequacy of ultrasound images
- Accuracy of documentation
- Sensitivity and specificity of screening ultrasound diagnosis
- Ongoing feedback to supervisors and sonographers.

### 2) Quality assurance (QA) activities

In order to ensure that the community sonographers are effectively imaging patients, the University of Washington will work with the Global Network to establish systems to review the community sonographers' imaging and provide a basis for the level of continued training necessary. The University of Washington will work with each of the Global Network sites to help tailor QA systems to the varying situations each site is likely to present. These systems will include a means of storing images of the community sonographers' scanning and of having these images reviewed by the sonographers at the referral facilities, the designated referral facility obstetrician or radiologist, and the University of Washington, to varying extents. These systems will also include periodic live reviews of community sonographer imaging in the field and at the referral facility. These reviews will be documented by the reviewer and assessed by the University of Washington. The University of Washington, in conjunction with the designated referral facility obstetrician or radiologist, will make recommendations to the Global Network as to the level of continued training necessary for the community sonographers at each site throughout the course of the study. The University of Washington, in conjunction with the designated referral facility obstetrician or radiologist, will similarly review the effectiveness of the sonographers at the referral facilities and make recommendations to the Global Network on actions necessary to establish and maintain a level of imaging proficiency in line with the intentions of the Global Network study Emergency Obstetric Care Training

Finally, as part of the QA process, each site will hold a refresher sonography training session (approximately 2-3 days in duration) approximately 6 months following the initial training. The objectives of the refresher training are to evaluate the retention of the skills of the trainees, identify and address any areas of weakness, and to ensure uniformity in understanding of the obstetric skills. This training also provides an opportunity to reinforce the study objectives and strengthen relationships with the referral hospital sonographers.

**Emergency Obstetric Care training**

The second component of the training will be of hospital staff in management of obstetrical conditions and will be performed at each site by a project obstetrician with skills in in-hospital training related to improving pregnancy outcomes and providing care for the major obstetric/neonatal conditions such as preeclampsia/eclampsia, obstetric hemorrhage, and newborn resuscitation. Obstetric/neonatal drills in the management of obstetric/neonatal conditions will play an important role in this training. The training will be concentrated in the initial 3 months, but we will plan for continual evaluation of hospital function and ongoing training to improve deficiencies noted.

## 1.8 Referral and Community Enhancement

There are two other important aspects related to the trial involving the local population.

### *1) Referral and System Enhancement*

This component will focus on working with government officials and health system and hospital administrators in improving health system management, especially since the success of the project

depends on a substantial level of integration of appropriate referrals between the health clinics and the hospitals. While this will not be a major component of the project, we expect to hold several sessions (and more if needed) with health system leaders and administrators to discuss integration of obstetric/neonatal care between the primary health clinics and the referral hospitals.

### *2) Community Sensitization*

Finally, as mentioned above, we plan to hold community orientations in each location where ultrasounds will be made available to ensure that all pregnant women are aware of the service, to know when and where it will be offered, and to be aware of the conditions ultrasound can diagnose and cannot diagnose, and the treatments for diagnosed conditions. The community will be informed that the ultrasound s are being made available to determine gestational age and to discover any pregnancy complication that might require referral to a higher level of care. We will also use this period to determine and address any barriers to receiving ultrasound at the community level. Depending on the community structure, the community notification portion of the intervention may overlap with some of the referral and transfer system analyses described above. For example, meetings in the intervention clusters may include government officials and hospital and health center administrators, all obstetric providers (physicians, nurse midwives, auxiliary nurse midwives), and, where applicable, community or traditional birth attendants, and health visitors not specifically doing deliveries or providing obstetric care. It will also, as stated above, include a series of ultrasound intervention cluster village meetings so that women and their families and village elders will understand the study and the potential of ultrasound to improve pregnancy outcomes.

Working with each site and after evaluating the capacity at the referral hospital, as needed, we may allocate a small amount of funds for crucial medical supplies and equipment including magnesium sulfate to prevent eclamptic seizures, and bag and masks for newborn resuscitation. The goal, however, would be to first work with the site to assess available local resources for medications and equipment. We hope to ensure that local resources are first utilized and to use grant funds only to supplement critical resources as needed.

The ultrasound units for the clinics and hospitals will be provided by GE Healthcare, through an in-kind contribution to the project. GE Healthcare will also provide maintenance for the machines for the duration of the project. GE Healthcare will also supplement this project through its own funds to provide all the support needed for the training and QA monitoring of the ultrasonographers. GE Healthcare will also provide the funds so that images of the ultrasound examination can be electronically transferred both locally and to the University of Washington for oversight and evaluation.

## 1.9 Economic Evaluation

With limited resources to provide maternal and child health services, stakeholders, including policy makers and donors, must make choices on which interventions to take to scale. An economic evaluation may provide stakeholders with some of the information necessary to choose interventions that are effective and efficient in improving pregnancy outcomes. Therefore, it is our intent to use data collected

during this study to perform an economic evaluation of the use of ultrasound in low-income country community settings if adequate funding for this evaluation is secured. Conditionally, we will develop an economic model for developing and implementing an ultrasound intervention in lower-income settings. We will consider clinical parameters, training considerations, outcome expectations, testing/evaluation, system infrastructure and logistical needs, as well as expected cost or financial variables. We also will consider costs from multiple stakeholder perspectives associated with community provider ultrasound training, monitoring, and the delivery of ultrasound care for pregnant women. We will assess these considerations from the perspective of the different countries participating in the study. The cost estimates will be described and compared to outcomes from the randomized trial associated with birth events such as the location of delivery and various clinical outcomes such as maternal, fetal or neonatal mortality, near miss maternal mortality, and interventions such as cesarean section, induction of labor and newborn resuscitation. A preliminary cost-consequence model will be developed and subsequently revised during the study period based on input from the Global Network team, expert advisors, and local principals. The modeling approach will allow estimation of costs compared to process endpoints, primary study endpoints, and other estimated health-adjusted outcome measures assessing survival time and quality of time. This evaluation will be performed under the direction of the project management committee in collaboration with members of the University of Washington training, evaluation and economic team. The cost analysis will be performed under the direction of the Global Network Steering Committee and the Project Management Committee. The analysis will focus on generic ultrasound equipment rather than specific manufacturer or any GE product.

# 2. Data Analyses Plan and Sample Size

## 2.1 Sample Size

The first primary outcome is a composite of four components including neonatal and fetal mortality, maternal mortality, and maternal near miss mortality. Within the Global Network, the neonatal and fetal mortality rates average about 27 per 1,000 births, the stillbirth rates average about 33 per 1,000, and the maternal mortality is approximately 2 per 1,000 births. We have not analyzed Global Network maternal near miss data, but several studies suggest that for every maternal death there are 5 to 10 near misses.(Almerie, 2010; Mustafa 2009; Okong 2006) Therefore, it is likely that the maternal near miss rate within the Global Network is 20 to 30 per 1,000 births. This estimate coincides with several developing country estimates of near misses ranging from 2% to 3% of all pregnancies. For sample size calculations we assumed a near miss rate of 25 per 1,000 births. Thus, our composite outcome baseline rate is estimated to be in the range of 80 to 90 events per 1,000 pregnancies with current care in the ultrasound and control clusters.

We are aware that a given pregnancy may have two composite outcome events such as a maternal death and a stillbirth. This overlap suggests that summing the rates to generate a composite rate size estimates may not be appropriate. However, because stillbirth and neonatal death are mutually

exclusive categories, as are maternal death and near-miss events, the overlap is unlikely to significantly reduce the estimated outcome event rates. We have estimated sample size for the two primary outcomes, using the existing (baseline) Global Network data from the African and Asian sites.

### Outcome 1: Composite Outcome Including Maternal, Fetal, and Neonatal Mortality and Near Miss Maternal Mortality

Figure 2 provides a graph representing the power assuming a risk of 80 per 1000 at 20, 25 and 30% reduction. If the underlying risk is 80 per 1000, then a total of 52 clusters (26 per arm) provide 80% power to detect a reduction of 20% in underlying risk and 58 clusters (29 per arm) provide 85% power, assuming an average of 750 births per cluster during the study period.

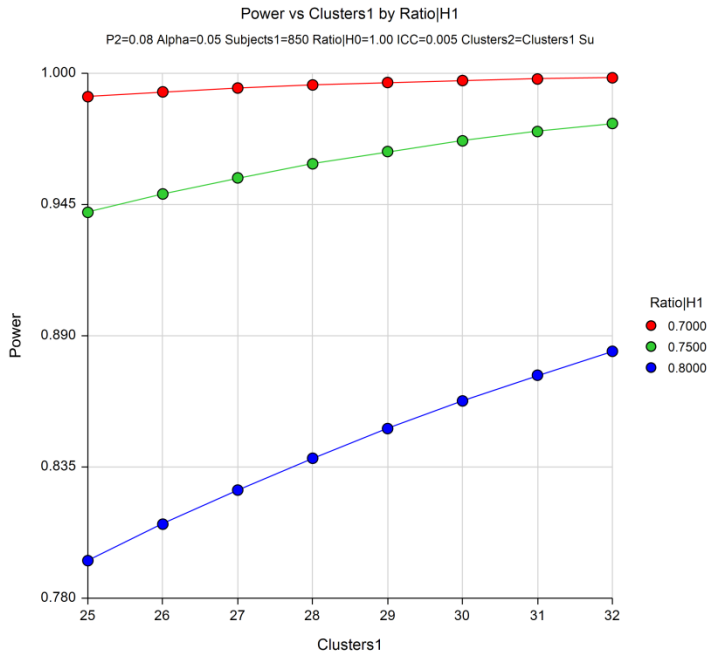


Table 5 provides sample size estimates for potential decreases in the composite maternal, fetal, and neonatal outcomes with 90% power and alpha at 0.05 for rates of the composite outcome in the range of 70 to 90 events per 1000 deliveries, target reductions of 20% to 25%, at ICC of 0.005 (a rate that is consistent with historic mortality rates in the Global Network clusters). Table 5 provides estimates of sample size based on various rates of the composite outcome, a 20% to 25% decrease in the primary composite outcome. Based on the information in Table 5, 58 clusters will provide 80% power to detect a 25% improvement in the composite outcome over a range of assumptions that are reasonable based on historic MNH Registry data; the design will provide 79% to 89% power to detect as little as a 20% reduction over the range of underlying risks.

**Table 5. Sample Size [WILL UPDATE]**

| Current Rate of Composite Outcome | Target Reduction (% decrease) | Target Rate for Composite Outcome | Number of Clusters per Arm Based on Different Assumed ICC* |
|---|---|---|---|
| | | | ICC=0.005 |
| 70/1000 | 25 | 52.5/1000 | 28 |
| 80/1000 | 25 | 60/1000 | 24 |
| 90/1000 | 25 | 67.5/1000 | 21 |
| 70/1000 | 20 | 56/1000 | 45 |
| 80/1000 | 20 | 64/1000 | 39 |
| 90/1000 | 20 | 72/1000 | 34 |

*Calculations assume 750 births per cluster; power = 80; alpha = 0.05

### 2.2.2 Outcome 2: Rate of Deliveries at Health Facility

Under the assumptions that the current utilization of health facilities for delivery ranges from 10% to 60% and that the ICC for hospitalization usage is no more than 0.02, which appear to be reasonable assumptions based on Global Network registry data, 10 clusters per treatment arm will provide at least 95% power to detect an absolute percentage increase in the utilization of delivery facilities for women with complicated pregnancies of 10% and a power of 98% or more to detect an absolute increase of 15% or more. Thus we will have sufficient power to evaluate increases in hospital utilization.

## 2.2 Data Analysis

In comparing baseline characteristics and key intervention demographic, clinical, and outcome measures across the clusters in the two treatment arms, descriptive statistics will include frequencies and percentages for categorical variables and means, standard deviations, and minimum and maximum values for continuous variables. Distribution of the variables will be examined to detect the outliers as a part of quality control and descriptive analysis of the data. Descriptive statistics will be tabulated for individual clusters and aggregated across clusters by GN site for the two arms. In addition, the frequency of missing data for critical variables (e.g., neonatal mortality, stillbirth, maternal mortality and near miss, ultrasound utilization, antenatal care, and referral frequency) will be examined for each cluster and by treatment arm for each GN site.

### 2.2.1 Primary Outcomes

As noted in Section 1.4, this study will address two primary hypotheses that involve distinct outcomes. We will test each of these hypotheses separately without adjustment for multiple comparisons.

The first of the two primary hypotheses will examine the effect of ultrasound implementation on a composite mortality and morbidity outcome that includes maternal mortality, maternal near miss mortality and stillbirth and neonatal mortality. The primary analysis, which will utilize data at the cluster level, will be based on an alternative to a classic randomization test recommended by Gail (1996) for cluster randomized trials that involve more than 30 clusters per treatment arm. The analysis involves a two stage approach. First, we will fit a linear model with the cluster as the unit of analysis and the composite mortality/morbidity rate for each cluster as the outcome measure. The model will include terms for GN site and randomization stratum nested within site; note that this model does not include a term for treatment. In the second stage of the analysis, the residuals from the first stage model and the t-test procedures described by Gail (1996) will be used to generate a hypothesis test of the difference in

composite mortality/morbidity and to generate 95% confidence intervals for the difference in this rate between the two treatment arms, controlling for GN site and randomization stratum.

One disadvantage of the approach describe above is that it doesn't provide for control of potential confounders other than those included in the randomization scheme, nor does it allow examination of potential differences by country. Consequently, we will conduct additional model-based analyses to assess whether the inferences generated by the randomization test are robust to control for potential confounders at both the cluster and individual subject level. Although this study is not powered to evaluate treatment by country interactions formally, any evidence of such interactions will be described through the model-based analysis of this primary outcome. Both the t-test analyses and the model-based analyses will be conducted using an intent-to-treat approach with clusters and individuals included in the analysis in the treatment arms to which they are assigned.

To facilitate the model-based primary analysis, we will evaluate baseline differences in key demographic and clinical measures between the intervention and control clusters to assess the extent, if any, of baseline imbalances between the two groups of clusters that might confound study inferences. If baseline differences between the treatment arms are identified, we will include appropriate cluster-level or individual-level variables in model-based analyses to evaluate the impact of these variables on the observed treatment effect. Because the primary interest is in the increase in the marginal morbidity/mortality rate at the cluster level, the generalized estimating equations (GEE) method of Liang and Zeger (1986) as implemented through the SAS procedure GENMOD will be used for the primary analysis. The model will control for cluster-level effects by assuming country-specific within-country correlation within clusters, and all inferences will be based on the empirical correlation matrix proposed by Liang and Zeger (1986). Additional details of the model will be specified in the Statistical Analysis Plan.

The second primary outcome includes the rates of prenatal care utilization and utilization of delivery facilities for women with complicated pregnancies. Although stated as a single hypothesis, it is our intent to evaluate each of these outcomes separately. We will address each of these two outcomes using the same two procedures that we described for primary composite morbidity/mortality outcome above.

### 2.2.2 Secondary Outcomes

In addition to the primary outcomes, the trial will address a number of secondary outcomes. The secondary outcomes include the difference between ultrasound and non-ultrasound clusters in rates of key mortality and morbidity outcomes including maternal mortality, maternal morbidity, early neonatal deaths, intra-uterine growth restriction-related mortality, and intrapartum stillbirth. These outcomes also include a number of process measures such as the proportion of facility deliveries and antenatal care utilization (including both the proportion of women with any antenatal care and the median number of antenatal care visits.

For each of these outcome measures, descriptive statistics will be computed as described in the introductory paragraphs above. Model-based analyses will then be used to examine the effects of the intervention on each of clinical and process measures. For the clinical measures, GEE models will be

used to evaluate the effect of the intervention on marginal risk of the outcome, with results reported for both unadjusted analyses and analyses controlling for covariates that differ across clusters. Additional details of the analyses for each of these outcome measures will be provided in the Statistical Analysis Plan.

## 2.3 Study Timeline

A six-month start-up period will include randomization, distribution of equipment, and the training and increasing initial community awareness of the ultrasound study. The start-up period will be followed by a three-month study pilot/ramp up period to ensure: (a) The study field sonographers are appropriately trained and are performing high quality scans; (b) The ultrasound exams and team are integrated into the clinic antenatal care system; (c) The referral system is functioning appropriately; and (d) The QC sonographer is in place to oversee the quality of the exams and the appropriateness of referrals. With the ultrasound clusters having at least 300 annual births, we anticipate the study enrollment period to be 18 months and the total duration of the field portion of the study to be a total of about 2 years to allow delivery and outcome collection for the last enrolled women. Using these assumptions, every ultrasound cluster should have a minimum of 500 deliveries over the course of an 18 month study. However, the study duration in each location will be determined by the sample size and the projected enrollment rate. Using baseline data, we anticipate that we will have sufficient data in the 24 month period of primary data collection to evaluate the primary question. The trial will be monitored by an established Data Safety Monitoring Committee (DSMC). If we run into unexpected delays or event rates, we will consult with the DSMC and NICHD staff to determine the range of possible solutions and then we will immediately notify the BMGF and GE Healthcare to determine the best course of action.

**Proposed Timeline**

1. **Six month preparatory phase** – development of materials including training manuals and a manual of operations, distribution of equipment, provide training and increasing community of awareness of the project. Initial 2-week obstetric sonography training to be completed.

2. **Three month pilot phase** - ensure quality of the ultrasound imaging performed for sonographers at the community health centers; ensure the referrals systems are in place and begin the community sensitization activities.

3. **18 month enrollment period** – primary outcome data collection

4. **Four month completion period** - While the enrollment period will be 18 months at each site, it could take another 4 months for the last person enrolled to deliver.

5. **Five month data edit/close-out** - Project data cleanup and project close out.

# 3. Organizational and Management

This trial represents an important collaboration between the NIH-funded Global Network, its foreign sites, the BMGF, and GE Healthcare, each contributing substantial resources to enable the project to be undertaken successfully. The Global Network was in fact originally initiated in 2001 as a collaborative partnership between the BMGF and the NIH with RTI serving as the data coordinating center. For this trial, Robert Goldenberg, a Global Network Principal Investigator, will be the scientific lead. Dr. Goldenberg is an obstetrician with more than 35 years research experience, including conducting studies in Zambia as well as leading a number of studies of the Global Network, including most recently a cluster-randomized trial to improve Emergency Obstetric and Newborn Care. Elizabeth McClure, a perinatal epidemiologist and the Principal Investigator of the Global Network data coordinating center, who has worked with the Global Network since its inception in 2001, will provide administrative oversight.

## 3.1 Global Network Study Investigators and Sites

The Global Network has been conducting single and multi-site studies to evaluate interventions to improve pregnancy outcome in developing countries since 2001. Since 2009, the MNH registry, a population- based registry of birth outcomes in 7 sites in 6 countries covers more than 60,000 pregnancies per year (Table 6). These sites are in many ways typical of countries in which they lie. Except for India, most births occur at home, and even in India, nearly 40% of births occur in a clinic or at home. The stillbirth and neonatal mortality rates are very similar to the rates reported in recent Lancet publications for the entire country. (Cousens, 2011; Liu, 2012)

| | Chimaltenango Guatemala | Lusaka Zambia | Western Provence Kenya | Thatta Pakistan | Belgaum India |
|---|---|---|---|---|---|
| **Study Clusters* (N)** | 16 | 10 | 12 | 10 | 16 |
| **Births 2009-2010 (N)** | 10,706 | 14,154 | 17,541 | 25,909 | 41,883 |
| **Birth attendant (%)** | | | | | |
| Physician | 27.9 | 2.7 | 1.6 | 22.7 | 56.5 |
| Nurse/midwife | 1.5 | 43.9 | 34.8 | 25.1 | 30.5 |
| TBA | 70.4 | 32.2 | 51.1 | 49.7 | 6.3 |
| Family/unattended | 0.2 | 21.2 | 12.5 | 2.5 | 6.7 |
| **Birth location (%)** | | | | | |
| Hospital | 26.0 | 5.7 | 9.5 | 24.3 | 61.5 |
| Health clinic | 3.1 | 42.0 | 25.6 | 23.3 | 24.3 |
| Home | 70.9 | 52.2 | 64.9 | 52.3 | 14.1 |
| **C-section rate (%)** | 11.4 | 1.0 | 1.1 | 6.6 | 8.7 |
| **Mortality rates/1000** | | | | | |
| Neonatal (28 day) | 27 | 22 | 16 | 45 | 25 |

| | | | | | |
|---|---|---|---|---|---|
| Stillbirth | 22 | 27 | 20 | 54 | 31 |
| Maternal mortality ratio/ 100,000, Mean | 95 | 211 | 88 | 239 | 187 |

**Table 6. Ultrasound Trial Site Characteristics**

*Number of study clusters that will be included in the ultrasound study

The MNH registry will serve as the data collection structure for this project. Together with the sites, RTI is responsible for maintaining and analyzing the data for the Global Network Registry. Research results from the Global Network have been published in NEJM, Lancet, and AJOG, among other journals.(e.g., Carlo WA, 2010; Althabe 2008; Derman, 2006) Furthermore, several of the Global Network sites have other Gates' funded research, including studies on intrapartum mortality, pre-eclampsia, nutrition, and newborn sepsis. Thus RTI, the Global Network, and the field sites have had an ongoing relationship of more than 10 years, and through other projects have an ongoing relationship with the Gates Foundation and GE Healthcare.

The Global Network sites, each of which has extensive experience conducting research, will undertake the ultrasound study. Each site has conducted a mapping exercise to determine the public, private and other health facilities including the health centers, district health hospitals and tertiary referral hospitals. The assessment of the health facilities included documenting the number/type of health providers, services provided and the current availability of ultrasound for obstetric services. Additionally, through the Global Network's ongoing MNH registry, each site has documented the number of pregnant women in the study catchment areas, the proportion who are currently seeking antenatal care, and the maternal mortality/morbidity and neonatal mortality/morbidity rates.

RTI has worked with staff at each study site to install data collection, data entry and transmission capabilities. From each site, remote access is possible and data are reviewed and transmitted on a weekly basis, with both on-site and central editing and review processes. RTI will provide study oversight and management of key elements of the study including data management and statistical analyses. RTI, a multidisciplinary research organization with projects in more than 40 countries, conducts basic and applied research in public health, epidemiology, genetics and biotechnical sciences and thus has a large pool of expertise to support research, as needed.

## 3.2 Management and Staffing Plan for this Project

The proposed study will be managed through RTI with Robert Goldenberg and Elizabeth McClure providing study oversight under the authority of the Global Network Steering Committee which includes members of the domestic and foreign sites and NICHD. Because of the collaborative nature of this study, an Ultrasound Study Management Committee consisting of Goldenberg and McClure; Bhala Kodkany, Hillary Mabeya, and Omrana Pasha representing the field sites; Caroline Signore and Marion Koso-Thomas of NICHD; Richard Derman of the GN protocol committee; and Robert Nathan of the University of Washington will provide study oversight. Rex Widmer of GE Healthcare will serve as Expert Consultant advising generally on healthcare technology issues in the developing world and study-related equipment issues. The BMGF will provide an ex officio member to this committee (Figure 3). Omrana Pasha, who has extensive experience with community work, will oversee community notification and other relationships for this project.

Global Network Investigators: Below we discuss study sites within the NIH-funded Global Network that will undertake the ultrasound study.

**Zambia**: The Zambia site is overseen by Dr. Elwyn Chomba (University Teaching Hospital, Lusaka, Zambia) in collaboration with Waldemar Carlo (University of Alabama at Birmingham). The site is based in Lusaka, Zambia, the capital, with study clusters located in the health districts surrounding Lusaka. A total of 16 clusters, with delivery clinics, surround University Teaching Hospital, the referral hospital for the catchment area.

**Kenya:** The Kenya site is overseen by Dr. Fabian Esamai (Moi University, Eldoret, Kenya) in collaboration with Ed Liechty (University of Indiana). Dr. Hillary Mabaye (Moi University) is the obstetrician who will be leading this study. The study management is based in Eldoret; with 16 study clusters based in Western Provence, a rural area approximately 2 to 3 hours' drive from Eldoret. Clusters each have a dispensary or health center with 2 district hospitals in the Provence, in addition to the referral hospital at Moi University.

**Democratic Republic of Congo:** The DRC site is overseen by Dr. Antoinette Tshefu (Kinshasa School of Public Health, Kinshasa, DRC) in collaboration with Dr. Carl Bose, Univeristy of North Carolina at Chapel Hill. The study management is based in Kinshasa, with study clusters and a coordination team based in Gemena, Equateur, a rural area. Study clusters each have a health clinic and those that are in the catchment area of one of 2 main referral hospitals (Gemena and Karawa) will participate in this trial.

**Pakistan:** The Pakistan site is overseen by Dr. Omrana Pasha (Aga Khan University) in collaboration with Dr. Robert Goldenberg (Columbia University, New York). The site includes 20 clusters in Thatta District, approximately 2-3 hour drive from Karachi, where the study team is based.

**Guatemala:** The Guatemala site is overseen by Dr. Ana Garces (IMSALUD) in collaboration with Dr. Michael Hambidge (University of Colorado Denver). The site includes 10 clusters located in Chimaltenango District, approximately one hour from Guatemala City. Clusters each have a health center where antenatal care is provided.

**RTI International:** RTI serves as the data coordinating center for the Global Network. Dennis Wallace is the senior statistician and Elizabeth McClure as the PI. For the Global Network, RTI has established data research units at each of the sites to enable data entry, security and transmission. RTI staff will develop data study manuals, forms, and perform data edits and analyses centrally, in collaboration with study investigators.

# 4. Adverse Event Monitoring

The following procedures will be followed for adverse event monitoring and reporting.

## 4.1 Definition of Serious Adverse Events

We do not anticipate any adverse events to be associated with ultrasound scans proposed in this study. However, because the outcome of the study includes adverse outcomes for the mother, fetus and newborn, we expect that there will be substantial numbers of adverse outcomes. We will evaluate these as part of the overall study. However, all serious adverse events potentially related to the ultrasound exam will be collected and reported. It has also been agreed that for this study fetal sex determination will not be performed and any project sonographer caught doing fetal sex determination scans will be removed from the project. For this project, disclosure of a fetus's sex will be a reportable event. A serious adverse event is defined for this project as any unanticipated, untoward medical occurrence related to ultrasound use causing physical harm to the mother or fetus that may arise during the implementation of this study.

All serious or unexpected adverse events will be reported, according to the reporting requirements.

## 4.2 Method of Reporting Adverse Events

All adverse event reports will be based on reporting guidelines as required by NICHD. This includes the notification of the occurrence of SAEs within specific timeframes:

Other serious and unexpected events must be reported within 7 days.

The SFI/ PI are responsible for ensuring that the following are notified within the appropriate timeframe:

- Appropriate local institutional review boards (IRBs);
- The Data Coordination Center (DCC) at RTI: all adverse events should be entered in the Data Management System (DMS) and transmitted within 24 hours [as a back-up, adverse events may be faxed to (202) 354 4787];
- The DCC will disseminate the report to the NICHD program official (and other NICHD staff as defined, e.g., the staff science collaborator) within one day.

# 5. Human Subjects

## 5.1 Institutional Review Board Review and Informed Consent Procedures

This protocol, as well as the informed consent documents and any subsequent modifications, will be reviewed and approved by the IRBs or ethics committees responsible for oversight of the study.

Regulatory Authorities

The study investigators will seek approval for the study from the appropriate regulatory authorities (i.e. Ministries of Health and ethical review boards) as required by international, national and local regulations. The study investigators will acquire all necessary approvals before beginning study activities. The study team will use methods such as meetings and posters to inform the community and its authorities about the purpose and procedures of the study. Women attending maternity health care services (antenatal care clinics, health centers, maternity hospitals) at intervention communities will be made aware of the study by placing informative posters in visible places.

Informed consent at the individual level

Pregnant Women:

Consent to collect data: In both the intervention and control clusters, data on antenatal care, pregnancy complications, maternal mortality, near miss mortality, stillbirth, and neonatal outcomes including neonatal mortality will be collected for all pregnant women and their infants. These data will be collected as part of the MNH registry and, therefore, additional consent for these data for the US study is not required. However, in the intervention clusters, additional data will also be collected from mothers who ultrasound exams. Individual informed consent will be obtained for the additional data collection as part of the consent process of the US study (See Appendix 3).

All eligible women will be provided with information about the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Informed consent procedures will be administered by the registry administrators and women will indicate approval either by signature or thumbprint. A written version of the consent form translated into the local language will be utilized. The woman will be encouraged to seek clarifications regarding the intervention and efforts will be made to ascertain whether she has comprehended the information. For patients who are illiterate, the text will be read in loud voice and written confirmation of consent will be obtained. The written confirmation will

be obtained as a left hand thumb impression in the presence of the woman's relative, who will attest to the process as a witness. The informed consent document is only a small component of the informed consent process. Adequate time will be provided for describing the study and fielding questions from the patient and/or immediate family members. Fair balance will be maintained while describing the risks and benefits of participation in the study. No undue pressure will be placed on the patient to enroll in the trial. It will further be explained that lack of participation will not affect the usual and anticipated standard of care.

Health providers

All health providers working in the intervention clusters that are eligible to be trained in the intervention procedures will be invited to receive the training and asked for their signed informed consent in order to obtain process measures on the quality of the training. (See Appendix 4) Those who decline to be trained will be able to continue attending to pregnant women as usual, and that the lack of participation will not affect their job in any way.

## 4.2 Participant Confidentiality

To maintain participant confidentiality, all evaluation forms, reports, and other records that leave the site will be identified by coded number only. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission from the participant, except as necessary for monitoring by the IRB, the NICHD, and the Office for Human Resource Protection (OHRP), local regulatory authorities, or the pharmaceutical supporters or their designee.

## 4.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the NICHD, within-country national health agencies, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected. The study will be monitored by the Global Network DSMC, which will make any recommendations regarding the continuation of the study to the NICHD.

# 5. Data Collection and Management

Data will be collected prospectively and will be kept confidential. The data will be collected in the local language using hard-copy forms, with only the individual study identification number on each form. The forms will be keyed into the computers at one or more selected central sites in each country. The hard-copy forms will then be retained in a secure location and will remain in that country.

Monthly audits and reports of incomplete data will be performed by a review team consisting at least of the SFI and the country coordinator. Data editing and error resolution will be performed monthly. These activities will be shared between the site and RTI.

Data will be entered into computers using the DMS developed by RTI. The DMS will also allow site staff to produce project reports and to back up the study database. At least once a week, deidentified data will be transmitted from the participating countries to the DCC at RTI. The DCC will conduct training on the DMS and will maintain the central database for the study.

All data that are collected at the clinic will be recorded using the data collection tools specifically developed for the study. Data forms will be sent daily to the in-country research office, where data entry computers are located, and entered in the DMS on a daily basis. After the form has been entered into the DMS, it will be placed into a folder labeled with the participant's unique subject ID. Data forms will be stored at the research unit's data entry center in locked cabinets. Only the SFI and project manager will have access to documents linking patient personal information to study ID code numbers, which will be kept in securely locked filing cabinets.

The data collection team will receive training from RTI on the proper completion of forms. They will be taught to mark only one answer choice for each question unless otherwise instructed; treat capital letters as instructions; record open-ended text legibly; record numbers and mark answers within the answer box; use the dd/mm/yyyy format to record dates; record time using a 24-hour clock; and to use a standard code, such as 99, to identify refusals or answers that are unknown. They will also be trained to affix properly the subject ID, to review forms for accuracy, and to safeguard the confidentiality of the form by keeping completed or partially completed forms in a secure, locked location. Preprinted study IDs will be provided by RTI. In addition to general instructions, question-by-question specifications for the survey instruments will be created by RTI. These specifications will provide specific instructions for complicated processes such as skip patterns or open-ended questions.

The weekly data transmission from the research units to RTI will be completed by using the BLAST system that is already installed on the data entry computers. This system provides a mechanism for sending secure data through the Internet. RTI will send an e-mail to the research unit to inform them if the transmission is not received.

The data entry software will be programmed to conduct range checks and simple consistency checks of the data. RTI will work closely with the study PI, SFI, and country coordinator in developing the edit specifications for the study data. This traps errors at the time of data entry, when the hard-copy form is available, and enables hospital and data entry staff to determine whether errors are due to keying or recording and to make the corrections. If the error is made in the recording of the data on the hard-copy form, the form is available and will be corrected before archiving. The data entry software permits staff to override an edit if there is a failure but the entered data are correct. An explanation will be expected in a comment field when this occurs.

Double data entry verification will be used to check for ID and data errors. Five percent of keyed records will be randomly selected and be rekeyed. The second entry will be completed by a person who did not

originally enter the data. Double-keying will take place at the research units. A correction report will then be generated and addressed locally. An error rate of less than 0.3% is considered acceptable. If the error rate is higher than acceptable, RTI will review the data and assess whether a member of the data entry team needs to be retrained.

When the data arrive at RTI, the data entry edits will be rerun and more extensive edits will be conducted. These batch edits will be run monthly, and copies of the edit failures will be sent back to the research units for resolution. The research units in each country are responsible for making all edits to the data in the DMS.

The DMS is password protected. It will require a user ID and password to be entered to ensure that only trained, authorized personnel have access to the data.

## 5.1 Data Closeout Procedures

Inconsistencies in the data will be resolved using the editing procedures described above. Any error that cannot be resolved will be documented and will include an explanation of why resolution was not possible.

At the end of the study, RTI will choose a 10% sample and ask the site to verify approximately 10 key variables related to the primary and secondary outcome by comparing the paper forms to the keyed data. The PI, SFI, and project manager will approve the main variables to be verified. If changes to the data are necessary, the site will make the necessary changes to the DMS and send written documentation of the changes to RTI. After the variables have been verified, RTI will lock the database. A copy of the final, locked database will be shared with the site. The final database will be accompanied by a codebook that describes variables and provides frequencies and summary statistics, instructions for how to merge files, documentation of subjects that were deleted from files and why, the protocol or manual of operations, a copy of study forms, and the question-by-question specifications.

At the close of the study, RTI will produce a final report, in collaboration with NIH and the PI. The final report will include descriptive and analytical tables, as well as text that explains the data set and the major findings in the tables.

# 6. Sustainability

The major question this trial seeks to answer is whether a technology, such as ultrasound, introduced into a low-income setting to strengthen a health system will result in improved pregnancy outcomes. During this trial, we will learn whether lower level providers can perform a relatively complicated medical evaluation with about 2-3 weeks of training, periodic QA activities, supervision, and retraining provided by a local physician and whether the knowledge gained is sustained over time. We will also learn if the health system strengthening accompanying the ultrasound training will be sustainable over the trial. Equally important, we will learn if the introduction of ultrasound will produce sufficient benefit

that health ministries, and donor agencies will opt to fund and support this technology in low-income countries.

To help ensure sustainability, the trial will use a short course training system that has been piloted and implemented in several low-resource settings. Furthermore, our approach - using one ultrasound team and one ultrasound machine to serve one or multiple health clinics - was chosen so that it could be reproduced in low-resource settings with manageable costs. While the specific costs of the ultrasound may vary, and we anticipate that the costs associated with the technology will reduce over time. An independent team at the University of Washington and GE Healthcare are actively seeking funding to formally evaluate costs for this project, but regardless, it is our intent to perform a cost analysis at the conclusion of the project.

If the trial demonstrates resultant reduction in maternal, fetal or neonatal mortality, we anticipate that the approach we have selected for the trial could be adopted and scaled up in low-resource settings. Furthermore, in each of our study sites, our study investigators work closely with the Ministry of Health in their respective health districts and thus will have access to the appropriate authorities for the presentation of the results. We emphasize that this study will be performed in government health clinics and referral hospitals, and in every site there will be at least local government support for the study. As the study progresses, each site will meet with regional and country health representatives to apprise them of the trial to determine potential for expansion of the use of ultrasound if the trial is successful. While the Global Network, GE Healthcare, and the BMGF are not likely or expected to provide continued support for this effort after the close of the project, it is our hope that, if it is successful and demonstrated to be cost-effective, the appropriate government agencies will include ultrasound in their overall obstetric care programs.

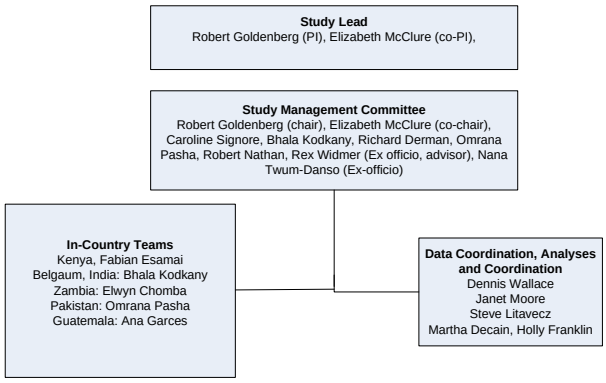


Figure 3. Study Organization

In summary, we believe this is an important trial for a number of reasons. Most significantly, it has the ability to demonstrate how an intervention such as ultrasound introduced with appropriate training and community and provider input and awareness can improve pregnancy outcomes in low income settings. It will also demonstrate how the Gates Foundation, a private company such as GE Healthcare, and a government entity, such as the NIH, can work together to evaluate the impact of such a technology.

# APPENDIX 1. DEFINITION OF NEAR-MISS (WHO)

The World Health Organization maternal near miss criteria: a woman presenting with any of the following life-threatening conditions and surviving a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy should be considered a maternal near miss case.

Clinical criteria:

- Acute cyanosis
- Gasping
- Respiratory rate >40 or <6/min
- Shock
- Oliguria non-responsive to fluids or diuretics
- Clotting failure

Laboratory-based criteria:

- Oxygen saturation <90% for >60 minutes
- Pa02/Fi02 <200 mmHg
- Creatinine >300 umol/l or >3.5 mg/dl
- Bilirubin >100 umol/1 or >6.0 mg/dl

Management-based criteria

- Use of continuous vasoactive drugs
- Hysterectomy following infection or hemorrhage
- Transfusion of >5 units red cell transfusion

(Say et al, 2009)

# APPENDIX 2. STUDIES ON OBSTETRIC ULTRASOUND IN LOW-RESOURCE SETTINGS

I. Capacity Development: Task shifting to paraprofessionals

A. Key learnings: Relevant facts, figures, observations, conclusions

i. Overarching context

- Ultrasound is operator dependent. It is simple to operate and equally simple to misinterpret (Mindel, 1997)
    - Expertise is not acquired via a manual or a textbook; those who use ultrasound require a long period of prolonged exposure
    - In one survey from Pakistan, for example, more than half of sonographers and radiologist who operator US had 'inadequate' knowledge (Akhtar, 2011)
- Effective obstetric imaging can be achieved by generalist physicians and midwives and may play an important role in achieving MDGs 4-5 (Maru, 2010)
- Persons with some medical knowledge such as nurse midwives could be trained to perform ultrasound examinations in a remote setting and could play an important role in triaging cases (Spencer, 2008)
- Health workers such as nurses with basic ultrasound training can perform Level I early pregnancy ultrasound examinations and fetal anomaly screening with high levels of accuracy (Hofmeyr, 2009)
- Local health workers can be trained to use ultrasound reliably and consistently to assess gestational age – Thai-Burmese border (Rijken et al, 2009)
    - Local trainees demonstrated a high level of agreement in measurement as compared with an experienced doctor
    - No tertiary education (grade 10); median age 20; 12 months minimum work experience
- ii. Training program content/length
- Training can be done in 3-4 days for limited obstetric functions (3-4 key issues) (PATH, 2009)
    - Pregnancy dating
    - Obstetric measurements
    - Multiple gestations
    - Fetal positioning
    - Broader basic training can be achieved in 2-3 weeks
- 3-day limited sonographic training for physicians (Harris, 2009)
    - Basic fetal positioning
    - Obstetric measurements
    - Placental location
- Basic sonographic pathology and anatomy can be taught to allied health professionals in the course of a 2-3 week training period (Harris, Marks et al, 2009)

    - Basic obstetrics
    - Gynecology (uterus, ovaries)
    - Abdominal exams (gallstones, hydronephrosis, bile ducts, etc)
    - Other simple techniques
    - Continuing education is essential
- 4-day intensive training for clinical officers/physicians in Tanzania (Adler et al, 2008)
    - Assessment of trauma
    - Abdominal
    - Hepatobiliary
    - Pregnancy (first trimester, pregnancy dating, fetal position)
    - Soft tissue
    - Echocardiography
    - Renal
- Five-year total sonographic training program for medical personnel occurs every 4 months, with modules lasting 2 weeks at a time- Tanzania (Ferraioli et al, 2007)
    - Total 30 weeks to cover basic through advanced/specialized sonography
    - Implication: 7-8 weeks to cover basic ultrasound
- Approximately 3 weeks devoted to obstetric functions of total 9 weeks comprehensive diagnostic ultrasound course (Shah et al, 2009)
    - Operating instructions
    - First trimester basics (evaluation of ectopic or molar pregnancy)
    - Methods for estimating gestational age
    - Evaluation of fetal position
    - Evaluation of cervix, placenta
- Important to include training in interpersonal skills for those who conduct ultrasound scans to communicate effectively with patients, address their concerns, and provide clear directives following ultrasound examination (Gonzaga et al, 2009)
- Important source of dissatisfaction with ultrasound among women was uncommunicativeness on the part of the operator and failure to reveal and explain fetal image (Tautz et al, 2000)
    - Provision of feedback found to be an essential factor in positively experiencing ultrasound
- Dire need for training of staff in social and communication skills (Tautz et al, 2000)
    - Even illiterate women expect to be informed and shown the screen and explained the image and examination results

iii. Instruction methodology

- The WHO Study Group on Diagnostic Ultrasound (1998) recommends the following number of scans to obtain proficiency (Maru et al, 2010):
    - 250 abdominal
    - 50 pelvic
    - 50 first trimester

    - 200 second/third trimester
- On-the-job training of midwives by rotating physicians (Maru et al, 2010)
- Learning on the job is more powerful than training conducted abroad (Ferraioli et al, 2007)
    - Different case mix and presentation of disease in developing vs. developed countries
    - Critical to provide training appropriate to environment in which trainees will work
- Evaluation programs must include clinical process indicators and outcomes measures (Maru et al, 2010)
    - # of diagnostic ultrasounds performed
    - number of safety checks
    - number of servicing events /visits
    - accuracy of diagnoses
    - outcomes of cases diagnosed
- 3 month course of practical training in obstetric ultrasound employed for nurse-level health workers – Thai-Burmese border (Rijken et al, 2009)
    - Based on WHO / BMUS training recommendations
    - All scans verified by senior sonographer
    - Written examination results
    - Evaluation of inter-observer and intra-observer variability
- Three stages of training from basic, advanced and specialized (Ferraioli et al, 2007)
    - Each course consists of 24 hours of didactic training, 36 hours of practice
    - Trainees receive either hard copies or CDs of training materials
    - Each course ends with written examination of 20-multiple choice questions (0.5 points each question) and a practical exam (evaluated on a 1-5 scale)
    - Candidates cannot progress to the next stage unless they achieve a score of at least 10 (7 written, 3 practical)
    - Goal of the program is to train the students to become trainers for self-maintenance
- Goal-oriented approach to ultrasound instruction- Tanzania (Adler et al, 2008)
    - Goal-oriented: Answers specific pre-determined clinical questions
    - Half-day sessions on didactic instruction on applications and knobology
    - Second half of day spent on conducting hands-on bedside evaluations of inpatients and outpatients at the relevant clinical site(s)
    - Each trainee had at least 20 supervised exams prior to independently performing
    - Logbook designed to capture data on clinical indication, findings, and demographics of patient
- Recommendations to strengthen training programs (Adler et al, 2008)
    - Longer training period
    - Frequent visits to reinforce training
    - Practical and/or written exams to assess skills
    - Transmission of images (by internet or mail) to reinforce clinical findings

- Training curriculum for physicians combined lectures and hands-on scanning sessions- in rural Rwanda (Shah et al, 2009)
    - Goal-directed ultrasound exams to answer specific clinical questions
    - Based on emergency medicine training programs in the U.S.
    - Taught by fourth-year emergency medicine resident who accompanied local trainees on daily ward rounds to demonstrate integration of bedside ultrasound into clinical practice
    - Hard copies of scans sent to US to undergo blinded review by physician to assess accuracy and quality

- iv. Certification / continuing medical education
- Medical schools in developing countries could organize a diploma in clinical ultrasound for local and regional health workers (Mindel, 1997)
    - Potential for WHO certification standards
- WHO has recognized the need for ultrasound scanning in developing nations and published a report in 1998 concerning the essentials, principles, and standards of training for allied health professional in ultrasound diagnostic imaging (Rijken, 2009)
- v. Key education challenges
- Frequent staff turnover leads to gaps in utilization and potential waste of training resources (Maru, 2010)
- Lack of technical capacity to conduct routine maintenance or repairs on equipment (Maru, 2010)
- No clear standard for training curriculum for paraprofessionals in diagnostic ultrasound

- II. Technology: Design features for rural requirements
- Overarching issues
- Key requirements for compact ultrasound in low-resource settings (Harris, Marks et al):
    - Lightweight (<10 lbs) but durable
    - Handheld transducer (between 2-5 mHz)
    - Measuring calipers on image screen
    - Power supply, rechargeable batteries
    - Service/maintenance available

- Rural clinics have limited power infrastructure (Maru et al, 2010) - Nepal
    - Lack of three-phase power transmission (single current, single phase)
    - Lack of large inverters or battery systems beyond 5-15 kW
    - Grid power subject to wide voltage fluctuations
- WHO has developed a basic radiographic system (BRS) which outlines the key technical recommendations for x-ray device and usage in low-resource settings (Adler et al, 2008)

- WHO has not yet developed a similar standard for ultrasound

ii. Hardware

a. Power

- Power requirements similar to laptop computer - Nepal (Maru et al, 2010)
    - 100 watt electrical rating supplied by 5 - 10+ amp outlet
    - Battery with several hours of life
    - Capable of being charged safely, effectively with voltage fluctuations
    - Resilient electrical cord and plugs

- Unreliable power sources in these regions; ultrasound should be chargeable from a variety of power sources (Harris, Marks, 2009):
    - Grid electrical outlet (120/220 Hz)
    - Solar (PV panel, rechargeable lead gel battery, 225W DC to 115V AC current inverter)
    - Vehicle cigarette lighter
    - Gas/diesel generators

- Sudden changes in power very common – Ghana (Spencer, 2008)
    - Current backup batteries only able to run for <2 hours before recharge
- Voltage stabilizer is key in low-resource settings owing to frequent electrical surges (Rijken et al, 2009)
- A voltage stabilizer is necessary to maintain constant voltage levels due to power inconsistency – Tanzania (Ferraioli et al, 2007)

b. Probe

- Approx. 3.5 mHz convex transabdominal transducer will have widest applicability for public health impact (Maru et al, 2010). High frequency linear probe best for procedural assistance
- 3.75 mHz probe utilized for obstetric ultrasound with health workers at Thai-Burmese border (Rijken et al, 2009)
- 3.5 mHz convex probe is utilized at a district hospital in Tanzania (Ferraioli et al, 2007)

d. Visualization

- One primary reason for women seeking ultrasound in Uganda is visualization of fetus for reassurance and bonding purposes (Gonzaga et al, 2009)
- Photographic prints: Running costs can be minimized by avoiding use of photographic printouts (Hofmeyr, 2009)

d. Connectivity

- Internet communications with radiology experts in other countries might be an adjunct to locally available medical resources (Spencer, Adler, 2008)

iii. Software

a. Algorithms/interface

- Ultrasound can automatically calculate gestational age, in weeks and days, from measurements based on Hadlock charts (Rijken et al, 2009)
    - Biparietal diameter (BPD)/ Health circumference (HC)/ Abdominal circumference (AC)/ Femur length (FL)
- Goal-directed instruction is taught in the context of emergency medicine to provide a discrete set or sequence of clinical questions to be answered during examination

Maintenance

- Maintenance of technology faces many issues in low-resource settings (Mindel, 1997):
    - Existing equipment is unreliable, poorly maintained, difficult to repair
    - Often cannot be utilized due to generators breaking down, power rationing
    - No spare parts available locally if equipment fails
    - When there is maintenance it is usually by expats on short-term contracts
    - Long delays in repairs and parts shipment and processing
    - Absence of preventative/diagnostic maintenance

III. Health System Integration: Linking detection to treatment

i. Overarching issues / Health system characteristics

- Ultrasound as a screening and diagnostic technology only has impact if effective and accessible services (surgery blood transfusion) are available to address problems identified (PATH, 2009)
- It is important to bear in mind that harm from inappropriate interventions following false-positive diagnoses could outweigh benefits from appropriate interventions following true-positive diagnoses (Hofmeyr, 2009)
    - The lower the risk of the population, the higher the proportion of false-positives
- Patients generally wait for extended periods before seeking medical care until diseases have progressed – Ghana (Spencer, Adler, 2008)
- Patients in low-resource settings delay seeking out care- caused by poverty, inadequate and unaffordable transport, hospital charges, mistrust of hospitals, and trust in traditional healers (Mindel, 1997)
- Key problem in low-resource settings (e.g., Thai-Burmese border) is that women do not remember their last menstrual period (LMP), and thus don't have an accurate indication of when they will give birth (Rijken et al, 2009)
- Women in developing countries acquire information about ultrasound from a variety of key resources based on their SES- Uganda (Gonzaga et al, 2009)
    - Women with higher levels of education cite sources such as radio, T.V. programs, newspapers, health promotion campaigns and peers/friends

- Women from lower SES cite information from local midwives, and peers/friends
- More likely to receive false/biased information from friends/peers (e.g., ultrasound can lead to cancer)

- Key reasons for obtaining ultrasound scans- Uganda (Gonzaga et al, 2009)
  - Fetal sex determination
  - Visualization of fetus (bonding)
  - Reassurance about viability
  - Ability to ask questions about fetus from doctor/sonographer

iv. Opportunities for ultrasound in antenatal care

- Key maternal/peri-natal conditions can be detected with ultrasound (PATH, 2009):
  - Ectopic pregnancies (only in first trimester)
- However, in developing countries most women initiate ante-natal care in second or third trimester
  - Date pregnancies (requires early scanning; not effective in third trimester)
- Reduce post-term pregnancies or unintentional pre-term inductions
  - Cephalopelvic disproportion, i.e., obstructed labor (pelvic measurements)
- Has limited sensitivity (30%) and predictive value (50%)
  - Placental problems; Placenta previa/ accrete (only in third trimester)
- Life-threatening but occur in only 0.3-0.5% of deliveries
- Not easily detectable with trans-abdominal ultrasound (better with transvaginal probe)
- Placenta previa can resolve itself until late pregnancy
  - Multiple gestations
- Detected clinically 50% of the time
- Not life-threatening to mother
  - Fetal malposition (breech and traverse lie)
- 2-3% of deliveries
- Detected clinically 50% of the time
- Only useful in late screening (37th week)
  - Fetal conditions
- Congenital abnormalities
- Intrauterine growth retardation
- Fetal heart rate

- 1998 systematic Cochrane Library review of nine trials found that early pregnancy ultrasound was associated with a reduction in twins being undiagnosed at 26 weeks, and induction of labor for post-term pregnancy (Hofmeyr, 2009)
  - Largest effect is the one trial from a low-income setting; confirmed in separate study done in South Africa

- Accurate gestational age estimation is crucial for rational management of severe pre-eclampsia and eclampsia (Hofmeyr, 2009)

- Biometry measurements in the second trimester have accuracy of ± 1 week in estimating gestational age, whereas accuracy decreases to ± 2 weeks in the third trimester (Rijken et al, 2009)
    - Variability in fetal biometry increases as fetus grows

- Core conditions utilizing ultrasound in resource-poor settings (Maru et al, 2010)
- Type Condition Intervention Skill Level Necessity
- Abdominal Cephalopelvic disproportion C-section Advanced Moderate
    - Ectopic pregnancy Surgical management Advanced Moderate
    - Retained products of conception Dilation and curettage Advanced High
    - Abruption placentae Medical/surgical management Advanced High
    - Peripartum hemorrhage Medical management Basic Moderate

- Pregnancy related studies (24%) accounted for largest category of ultrasound exams following introduction of portable ultrasound into refugee camp in Tanzania (Adler, 2008)
    - Key usage was for pregnancy confirmation and staging
    - Tracking progression of pregnancy
    - Incidental detection of twins
    - Fetal demise

- Obstetric scans (30%) were the most frequently used application of ultrasound after introduction of ultrasound into two district hospitals in rural Rwanda (Shah et al, 2009)

- Obstetric scans (9%) were the second most frequent application of ultrasound after a portable ultrasound was introduced to 2 primary care sites and 2 hospitals in a community in Ghana (Spencer, 2008). OB scans represented over 50% of scans in the primary care setting

- Notable clinical value of portable ultrasound in low-resource settings – Ghana (Spencer, 2008)
    - Of 67 ultrasound exams, 81% abnormal findings, 81% added to clinical diagnosis, 40% influenced clinical decision/outcome
    - Portable ultrasound sufficient to detect findings that were abnormal and generally not subtle

- Changes in patient management plans based on ultrasound exams primarily centered around surgical procedures- rural Rwanda (Shah et al, 2009)
    - Cesarean sections following diagnosis of breech position of fetus, placenta previa, multiple gestations
    - Dilation, curettage procedures after diagnosis of retained products of conception with females showing symptoms such as bleeding
- Ultrasounds also useful for diagnosing musculo-skeletal problems in neonates stemming from gestation or birth injuries – Ghana (Spencer, Adler, 2008)
    - However this would require further training in other ultrasound methods and technologies (different probe, frequency)

v. Secondary benefits

- Psychological benefit to women of real-time sonography of their fetuses cannot be overestimated (Hofmeyr, 2009)
    - Most women found it a positive experience, and appreciated the opportunity to see their baby

- Women who come to a health facility for an ultrasound can be supplied with a prenatal care package, and the availability of ultrasound may incentivize women to seek care earlier (Hofmeyr, 2009):
    - Iron/folate supplementation
    - Syphilus treatment
    - Calcium supplements for pre-eclampsia
    - Cervical cerclage for cervical incompetence
    - ARVs for HIV
    - Malaria prevention
    - Treatment of infections (urinary, etc.)

vi. Key integration challenges

- Late presentation of cases causes complexities in referral; if found earlier, would have simpler and more practical treatment regimens (Spencer, 2008)

- In a low-resource setting, the risk is great when limited resources are diverted away from other highly-effective interventions (Hofmeyr, 2009)

- Health workers admitted that they were less rigorous about taking histories and conducting clinical examination after the introduction of ultrasound; over-dependence on ultrasound (Tautz, 2000)

- No consensus on appropriate use of compact ultrasound for obstetric care with regard either to the timing of scans, the best location for scans, or the appropriate target group (PATH, 2009):
    - Early, mid, and/or late pregnancy?
    - Referral hospital, peripheral facility, or periodic outreach to villages?
    - All pregnant women or a selected high-risk or symptomatic group?

- Evidence from key studies does not support measurable impact on maternal or perinatal mortality or morbidity associated with routine ultrasound screening of pregnant women (PATH, 2009)
    - In resource-constrained South African peri-urban health district, researchers found no significant difference between women who had ultrasounds and who didn't in terms of key health outcomes (Van Dyk, 2007)
    - Cochrane Library review: routine late ultrasound (without clinical indicators of risk) did not benefit mother/baby
    - Ghana study: ultrasound does not reduce maternal mortality or perinatal mortality. But potentially useful for reducing referrals and diagnosing antepartum hemorrhage.

- Maintaining quality control in antenatal ultrasound service is essential to ensure data obtained are clinically meaningful (Rijken, 2009)

- Potential for excessive misuse of obstetric sonography when it is not justified due to its commercialization for monetary gains for health workers (Gonzaga, 2009)

- Ultrasound can contribute to over-medicalization of pregnancy; re-conceptualization of pregnancy being organic and healthy to being medical problematic or sickening (Tautz, 2000)

*Note: Review compiled by GE Healthcare*

# APPENDIX 3. SAMPLE CONSENT FORM FOR WOMEN RECEIVING ANTENATAL ULTRASOUND TO IMPROVE PREGNANCY OUTCOMES

**TITLE OF RESEARCH: First Look: Ultrasound use to improve pregnancy outcomes in low income country settings**

**A cluster-randomized trial of the NICHD Global Network for Women's and Children's Health Research with support from the Bill and Melinda Gates Foundation and GE Healthcare**

**INVESTIGATORS:**
XXXX

**SPONSORS:** The Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), The Bill and Melinda Gates Foundation and GE Healthcare

**Researchers' Statement**
We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When all your questions have been answered, you can decide if you want to be in the study or not. This process is called 'informed consent.'

**Purpose of the Study**
We want to improve the health of pregnant women and newborns. We want pregnant women to receive ultrasound procedures during pregnancy. The images will help us know if a pregnant woman has a risk for the pregnancy or delivery.

**Study Procedures**
You will have your standard clinical care at the health center. If you choose to take part in this research study, we will also perform ultrasound procedures. Ultrasound produces images of your baby. The health provider will slowly move a type of camera over your belly. The pictures will show how many babies you have, where the baby is in your womb, and your baby's age. Images may also indicate problems with a pregnancy. You will be able to see the image of your baby during the procedure. We will give you an image of your baby to keep.

You will have 2 ultrasound procedures. The first will be performed at 18-20 weeks and the second will be at 32-36 weeks. The ultrasound procedures will take place at a regular clinic visit. Each ultrasound procedure will take about 10 -20 minutes. We will use information from the images for our study.

We may refer you to a hospital for your clinical care, if needed. The hospital has equipment and special healthcare for women at higher risk. We want you to have the best care possible for your pregnancy and delivery.

We will record information from your medical records at the health center and the hospital. We will record information about your pregnancy (clinic visits and lab results), delivery, complications, treatments and outcome. We will also record information about your baby.

**Risks, Stress, or Discomforts**
There are no known physical risks for the ultrasound procedure. Some people do not want to take part in research.

**Alternatives to Taking Part in the Study**
If you choose not to take part in this study, we will not perform an ultrasound and will not record information from your medical records. And in that case, you will receive the standard health care from this health center.

**Benefits of the Study**
We will not pay you for taking part in this study. You may benefit by you and your health care providers having more information about your pregnancy. We hope to identify pregnancy risks. We want to help pregnant women have safer pregnancies and deliveries in the future.

**Confidentiality of Research Information**
Information about you is confidential. We will assign an identification code to the study information. We will keep the link between your name and the code in a separate, secured location until August 1, 2015. Then we will destroy the link. If we publish the results of this study, we will not use your name.

Government or university staff sometimes reviews studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

**Other Information**
We have given you information about the project called "First Look: Ultrasound use to improve pregnancy outcomes in low income country settings." We have discussed the risks and benefits of the project and you understand that you do not have to agree to be in the project or may decide later not to be part of the project. This will not affect your baby's care in any way. If you have any questions, please call [insert senior investigator/ethics committee].

---

**Signatures**

*Person requesting consent, please check applicable boxes:*

- ☐ Consent obtained (for adult respondent)
- ☐ Assent (for minor respondents)
- ☐ Permission from family member of minor respondent

Agreement to have ultrasound exams (Please check one of the following boxes):

- ☐ Yes, I agree

□ No, I do not agree.

I have read the consent form or the consent form has been read to me. I understand the contents and the signature or sign below confirms that I agree to participate in this study. (The participant will receive a copy of this form.)

_____

Signature or thumbprint of participant or Legally authorized representative — Date

_____

Signature of father of the baby (if reasonably available) — Date

_____

Signature of researcher — Date

May we contact you for future studies by our study staff? □ Yes □ No

# APPENDIX 4. SAMPLE CONSENT FOR HEALTH PROVIDERS TO BE TRAINED IN ANTENATAL ULTRASOUND

**TITLE OF RESEARCH: First Look: Ultrasound use to improve pregnancy outcomes in low income country settings**

**A cluster-randomized trial of the NICHD Global Network for Women's and Children's Health Research with support from the Gates Foundation & GE Healthcare**

**INVESTIGATORS:**

XXXX

**SPONSOR:** *The Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD), The Bill and Melinda Gates Foundation and GE Healthcare

## Researchers' statement

We are asking you to be in a research study. The purpose of this consent form is to give you the information you will need to help you decide whether to be in the study. Please read the form carefully. You may ask questions about the purpose of the research, what we would ask you to do, the possible risks and benefits, your rights as a volunteer, and anything else about the research or this form that is not clear. When all your questions have been answered, you can decide if you want to be in the study or not. This process is called 'informed consent.'

### Purpose of the Study

We want to improve the health of pregnant women and newborns. We will train midwives to perform ultrasound procedures. We hope ultrasound images will help us identify potential risks for pregnancy and delivery.

### Study Procedures

If you choose to take part in this study, you will undergo a course in performing ultrasound imaging procedures. This is a 10 day course with about 46 hours of instruction:

| DAY # | LECTURES | HANDS-ON SESSIONS |
|---|---|---|
| 1 | • Introduction to the Course<br>• Physics and Knobology<br>• Tomography | • Introduction to the Equipment<br>• Transducer Orientation and Tomography<br>• Interpreting Structures |

| | | |
|---|---|---|
| 2 | • Infection Prevention and Control (IPC)<br>• 2nd and 3rd Trimester Anatomy<br>• Fetal Dating: 2nd and 3rd Trimesters | • The Patient<br>• Preparing to Scan<br>• ROBUST Technique |
| 3 | • Pelvic Anatomy<br>• 1st Trimester Anatomy<br>• Fetal Dating: 1st Trimester | • Non-pregnant Pelvis<br>• Biometry |
| 4 | • Amnionic Fluid<br>• Placenta | • Amnionic Fluid<br>• Placenta<br>• The Cervix<br>• ROBUST and Biometry Practice 1 |
| 5 | • Fetal Malposition | • ROBUST and Biometry Practice 2<br>• Fluid, Placenta and Cervix: Practice<br>• Introduction to 2nd/3rd Trimester Screening Ultrasound<br>• Screening 2nd/3rd Trimester Ultrasound |
| 6 | • Review Week 1<br>• 1st Trimester Pain and Bleeding | • Screening 1st Trimester Ultrasound<br>• Screening Ultrasound Practice |
| 7 | • Ectopic Pregnancy<br>• Multiple Gestation Pregnancy | • Screening Ultrasound Practice |
| 8 | • Intrauterine Growth Restriction<br>• Fetal Anomalies | • Biophysical Profile<br>• Screening Ultrasound Practice |
| 9 | • Case Study #1 No Cardiac<br>• Case Study #2 Breech | • Screening Ultrasound Practice |
| 10 | • Case Study #3 Bleeding<br>• Case Study #4 Blighted Ovum<br>• Case Study #5 Previa | • Practical Testing |

We want to measure what trainees learn during the course. So we will give you a test before you take the course, and then give you the same test after you complete the course. We will also give you a practical skills examination at the end of the course.

After completing the course, you will perform ultrasound procedures during pregnant patients' clinic visits. Prior to performing the ultrasound, you will ask patients to allow you to perform the ultrasound on a voluntary basis. At first the ultrasound procedures will take about 20 minutes. As you gain experience, the ultrasound procedures will take less time, about 10 minutes.

We ask you to record the findings on each obstetric patient: fetal position, fetal number, placental position, and measurements. You will save images on the ultrasound machine.

You will refer patients who are "at risk" to the hospital for clinical care.. Each patient sent to the referral hospital will have ultrasound procedures by a radiographer. We will compare your recorded findings and measurements with the hospital radiologists' findings.

## Risks, Stress or Discomfort

There are no physical risks for taking part in this study. You will be paid your usual salary during the course. The ultrasound course is intensive. You may experience some stress in completing the course and performing a new procedure. If you cannot complete the course, your employment at the health center will not be affected.

### Alternatives to Being in the Study

If you choose not to take part in this study you will not be trained to perform ultrasound examinations. Your employment at the health center will not be affected.

## Benefits of the Study

You may benefit from taking part in this study. You will learn a new skill. The new skill and experience may improve your opportunities for employment in the future.

We hope ultrasound procedures help identify pregnant women with higher risk for labor and delivery. We hope this study results in safer deliveries in the future.

### Confidentiality of Research Information

The researchers will keep the study information confidential. The researchers will assign a unique study code to all of your study information. We will keep the link between your name and the code in a separate, secured location until XXX. Then we will destroy the link. If we publish the results of this study, we will not use your name.

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

## Other Information

_____

We have given you information about the project called "First Look: **Ultrasound use to improve pregnancy outcomes in low income country settings**". We have discussed the components of project participation and project training and you understand that you have the option to participate or decline, without any negative consequences to your work.

**Signatures**

Agreement to participate in antenatal ultrasound training and implementation (Please check one of the following boxes):

- ☐ Yes, I agree to participate in antenatal ultrasound training and implementation.
- ☐ No, I do not agree to participate in antenatal ultrasound training and implementation.

I have read this form/this form has been read to me. I understand the contents and the signature below confirms that I agree to participate in project training and implementation. (The participant will receive a copy of this form).

_____

Signature or Thumbprint of Participant or Date

Legally Authorized Representative

_____

Signature of Researcher Date

May we contact you for future studies by our study staff? ☐ Yes ☐ No

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