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KHON KAEN UNIVERSITY

**A RANDOMIZED CONTROLLED TRIAL FOR
THE EVALUATION OF A NEW ANTENATAL CARE MODEL :
A MULTICENTER WHO STUDY**

A REPORT FROM THAILAND

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August 26, 1998.

Dr. Marge Koblinsky
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U.S.A.

Dear Marge,

My colleagues and I are very pleased to submit our report for the "randomized controlled trial for the evaluation of a new antenatal care model : a multicenter WHO study" conducted here in Khon Kaen, Thailand. This study was kindly support by MotherCare, Subcontract No. 5024-32.

My colleagues and I would very much appreciate it if you and your colleagues could kindly give comments and suggestions.

We are waiting for the data from the other 3 sites to be combined and analysed centrally in Geneva before the meaningful evaluation of a new model of antenatal care can be drawn.

Many thanks again for your generous support and I look forward to hearing from you.

With best wishes.

Yours sincerely,

Pisake Lumbiganon, M.D., M.S.
Principle investigator.

c.c. Dr. Jose Villar, HRP/WHO, Geneva

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1. EXECUTIVE SUMMARY

Antenatal care programmes as currently practised originate from models developed in Europe in the early decades of this century. The number of visits and the core activities remain practically unchanged and unevaluated, and new technologies which have been incorporated have seldom been scientifically assessed. Furthermore, the coverage of this traditional antenatal care in developing countries is very low and tends to be used by those women at lowest risk. It is unrealistic to expect that these countries will be able to expand this model of antenatal care to cover all women. A recent UNFPA report (Sakik, 1991) recognized that the required increase in the coverage and quality of MCH/FP services will have to be reached within the existing strategies and technologies and will likely have to be achieved with less than adequate resources. Hence, there is an urgent need, particularly in developing countries, for the evaluation of antenatal care effectiveness and for the study and identification of a scientifically proven package which can be offered to all pregnant women in these countries. This will complement efforts being made to evaluate specific perinatal activities.

The World Health Organization and collaborating institutions in developing countries have started conducting a randomized controlled trial to evaluate the impact of an improved and rational programme of antenatal care on the health of mothers and newborns. The duration of the entire study is 51 months.

The antenatal care programme presently in use in developing countries varies from one site to another, but is usually based on developed countries' practices. The recommended number of visits is typically eight to twelve, although the actual average number for those who attend at all will be closer to four.

The core of the new, improved programme of antenatal care consists of four visits which include only activities scientifically demonstrated to be effective in improving pregnancy and maternal and newborn outcomes. Specific interventions are included in each of these four visits. Health education and information for the mother are a part of each visit, stressing the

danger signs of complication during pregnancy and actions to be taken should they occur. The protocol specifies tests to be done at each visit and the specific actions for the different test results.

The proposed study enrolls approximately 5,000 women in each of four institutions over an average period of 18 months. There are a total of 56 antenatal care units, randomly allocated to provide either the new programme of antenatal care or the programme presently in use. Each group of antenatal care units is expected to be similar in terms of number of clients served, population characteristics (race, ethnicity, religion, socio-economic status, general health conditions), and levels of perinatal outcomes. Women are recruited as they present for antenatal care.

The two programmes of antenatal care will be evaluated in terms of severe maternal and perinatal morbidity. Since maternal mortality is a rare event, it is not feasible to conduct a study to demonstrate an impact of health care on it, and surrogate measures will therefore be used. The sample size calculation is based on the anticipated impact on selected maternal and newborn morbidity indicators. (Assuming that these indicators will have on average an incidence of 100 per 1,000 live births in participating centres, the study is designed to detect a 18% change).

The impact of the two programmes on maternal health will be compared in terms of specific morbidities, their severity, and general measures of morbidity, such as days in hospital and amount of resources consumed during hospital stay.

The impact on neonatal health will be assessed in terms of perinatal and neonatal morbidity, birth weight, gestational age and incidence of specific morbidities, as well as more general measures of neonatal status such as days in special care, including intensive care (where available), condition at discharge and hospital resources consumed. Where there is evidence that the resources required by the programmes differ, the cost effectiveness of programmes of care will be evaluated in different settings.

In addition, the two programmes of antenatal care will be compared in terms of process variables, such as average duration of contact between patient and care provider, average waiting time of patients, cost of antenatal care per pregnancy, patient and provider satisfaction with the services and perceived quality of care in a random sample of the population studied.

The study is coordinated by WHO in collaboration with the local institutions in Argentina, Cuba, Saudi Arabia and Thailand.

If the new programme of antenatal care is found to be more effective in preventing neonatal and maternal morbidity, and/or it is found to be less expensive than the traditional programme at the same level of pregnancy outcome, considering that users and providers are more satisfied with the new model, WHO will develop and circulate recommendations for antenatal care to governments and other agencies. It is expected that the new system will allow countries to maximize their resources and concentrate them in the most rational and effective way.

This report describes a descriptive result of a study conducted in Khon Kaen, Thailand.

This is a part of a large multiclinic, multisite, cluster randomized controlled trial. The other 3 sites include Rosario, Argentina, Havana, Cuba and Jeddha, Saudi Arabia. Twelve antenatal care clinics in 12 district hospitals were randomly assigned into 2 groups. Six clinics in the intervention group offered a new model of antenatal care while the other 6 clinics in the control group offered a traditional antenatal care. Recruitment of subjects was from May 1, 1996 to April 30, 1997. Follow up of the recruited subjects was done until October 31, 1997. All the data were entered and updated by the local coordination unit in Khon Kaen and transferred monthly to WHO in Geneva by e-mail. The expected number of subjects from Khon Kaen, Thailand was 6000. The total sample size from 4 sites was about 20000 subjects.

Six thousand seven hundred and sixty five subjects were recruited, 3449 and 3316 subjects in the intervention and control groups respectively. There were 182 missing subjects, a rate of 2.7%, leaving 6583 subjects for data analysis. Among 3379 subjects available for analysis in the intervention group, 3053 (90.3%) subjects were classified to be low risk and eligible for a new basic antenatal care model. The average age was 24.5 years with 18.7% teenage pregnancy. A majority of subjects attended primary school education. There were very few subjects who smoked or used known substance abuse. About 40% of subjects were primigravida. Rh isoimmunization was very rare. There were 182 (2.7%) abortions. More than 90% of the subjects received completed tetanus immunization. Most subjects (95.7%) received iron supplementation. During antenatal care, 144 (2.3%) subjects were referred to a higher level of care, while 180 (2.8%) subjects required antenatal hospital admission. The prevalence of severe anemia (Hb < 90 g/l) were 4.7% and 6.4% in the antenatal and postpartum period respectively. There were 113 (1.8%) subjects with severe urinary tract infection. There were 60 (0.9%) subjects with pregnancy induced hypertension (PIH) but only 26 (0.4%) required treatment. The incidence of maternal morbidity index indicator* was 8.3%. The low birth weight rate was 9.0%. Eight women died, giving a maternal mortality rate of 0.12%. There were 6400 births with 100 (14.5/1000) fetal deaths and 42 (6.7/1000) neonatal deaths. The perinatal mortality rate was 22.2 per 1000 births.

The result of the comparison between the new antenatal care model and the traditional model will be submitted to MotherCare when data from the other 3 sites are available and combined for statistical analysis which is expected to be available in late 1999.

* Maternal morbidity index indicator is defined as the presence of one of the following severe maternal conditions : proteinuric - preclampsia, eclampsia or severe hypertension (> 160/110 mm Hg) during pregnancy or within 24 hours of delivery; postpartum anemia < 90 g/l of hemoglobin and severe urinary tract infection/pyelonephritis, defined as requiring antibiotic treatment or hospitalization.

2. INTRODUCTION

Antenatal care programmes, as currently practised, originate from models developed in the early decades of this century in Europe, notably the UK. The core of these early models remains practically unchanged in current programmes, although, as medical knowledge and technology have evolved, new technologies for screening for disease and primary and secondary prevention have been added to routine antenatal care in developed countries. Unfortunately, these new components and the timing of visits have most often been introduced without proper scientific evaluation (Rosen et al., 1991; Fink et al., 1992; Johnstone et al., 1993).

These models for antenatal care contain a substantial number of visits for the mothers – as many as 16 visits – with little or no distinction between high and low-risk mothers. Recently, cost-benefit aspects of antenatal care have been addressed in several countries, and attempts are being made to reduce costs for clients and the health care services (Anon, 1986; Rosen et al., 1991).

To a large extent, developing countries have in theory adopted the antenatal programmes of the developed countries with only minor adjustments pertaining to endemic diseases. In many of these countries where resources for reproductive health care are sparse or used less than efficiently (Sundari, 1992; Fathalla and Rosenfield, 1992) and fertility rates are still high, the cost benefit of antenatal care as practised must be questioned. The care often consists of irregularly spaced visits with long waiting time and poor feedback to mothers, and there is little communication between the antenatal care clinics and the obstetric departments and maternity units.

Because of time constraints, the visits tend to be of a ritualistic nature rather than rational health care, as is demonstrated by recent evaluation of the activities of prenatal care in three large maternities in Latin America (Kestler, 1992). Normal pregnant women spent an average of 62 to 228 minutes in the clinics, with only nine to twelve of those minutes with the doctor. The doctor's interview lasted a mean of five minutes. No time is routinely

devoted to activities of women's most important concerns, such as the explanation of procedures and involvement of mothers in these procedures (Drew et al., 1989). However, in most developing countries, women attending prenatal care do not receive all the benefits possible from these visits. For example, tetanus immunization is not provided to a large proportion of women attending prenatal care although this is recommended in all programmes (Buekens, 1990; Buekens, 1995).

For most developing countries, the validity of the content and the rationale for frequency and timing of visits have not been evaluated at all. The few observations made have questioned the impact of antenatal care on maternal and perinatal morbidity and mortality (Moller et al., 1991; Rooney and Graham, 1991). It is worth noting that the lack of evaluation of antenatal care is not exclusive to developing countries (Starfield, 1985). The recent US Public Health Service Expert Panel on the Content of Prenatal Care noted in their review "the literature on prenatal care activities was often limited, and many studies were conducted without maximal scientific rigor" (Rosen et al., 1991). Similar conclusions were made by the European panel (Lindmark and Crattingius, 1991).

The need for randomized controlled trials on procedures and examinations included in currently practised antenatal care, has been identified (Steer, 1993). A recent extensive review of the literature concluded that "carefully controlled evaluations of the content, number and timing of prenatal care visits for women with differing medical and social risk are essential" (Fink et al., 1992). Such trials can establish minimal levels of care for women at low risk through comparison with less frequent or less intense prenatal care to standard care (Fiscella, 1995).

The means whereby antenatal care prevents maternal and perinatal mortality and morbidity is logically complex. Few of the procedures commonly undertaken during antenatal care have a major impact on morbidity or mortality, and some may have no effect. For others, there can be no impact unless other elements are also in place and functional; for example, identifying preeclampsia has no impact unless affordable and effective treatment is instituted or available; identifying the risk of postpartum hemorrhage has no impact if

institutional delivery is not sought, unavailable or ineffective. To further complicate the evaluation of the effect of prenatal care on perinatal mortality, there is a different effect across populations. In Indonesia, among normal birth weight infants, prenatal care had more impact on perinatal mortality than maternal education, used as an a priori indicator for socioeconomic level (Bernard & Sastrawinata, 1985). Conversely, in New York City, prenatal care has less impact on perinatal mortality than maternal education (Paneth et al., 1982).

Epidemiological studies tend to show that women who receive antenatal care have lower maternal and perinatal mortality (U.S. Congress, 1988; Greenberg, 1983; Fiscella, 1995). Epidemiological studies have also shown that there is an association between the number of prenatal visits and gestational age at the initiation of care with pregnancy outcomes after controlling for confounding factors, such as length of gestation (Gortmaker, 1979; Ryan, 1980; Quick, 1981).

Because of this relationship in non-controlled studies, the importance of antenatal care in preventing mortality and morbidity is emphasized. Because of the suggested dose-response effect, many maternal health programmes seek to increase the quantity of antenatal care provided. Recently, however, attention has been given to the essential elements of the prenatal care package, in an effort of ensure that quality is not overlooked in favour of quantity. Consideration is also being given to whether more effective antenatal care could be provided with fewer visits, and when these fewer visits are focused on the elements most likely to have an impact on mortality and morbidity; in other words, to stress quality at the expense of quantity. In principle, this should be more effective as well as less expensive. Emphasis is made on the evaluation of a comprehensive package of antenatal care, rather than individual clinical interventions, because evidence demonstrates the disparities in pregnancy outcomes between social group are due to all major maternal conditions and not to single pathologies (Kempe, 1992). Furthermore, the interactive nature of antenatal interventions and the multicausal characteristics of the leading negative outcomes to be prevented point toward a multiplicative effect of the components of antenatal care.

The concept of antenatal care has been generally recognized as a very good model of preventive health care. In theory, a series of health examinations with predefined content should enable health personnel to uncover ailments and other conditions in the mother and her fetus(es) which may threaten the pregnancy and its outcome. The conditions may then be treated or monitored to secure a better outcome. Planning for a safe delivery is an integral part of antenatal care. In a wider context, antenatal care should embrace the social environment, as well as the medical aspects of pregnancy. It is also one of the few situations in which healthy women will have contact with the health care system, allowing for other preventive interventions (Rosen et al., 1991).

In currently applied antenatal care programmes, the basic philosophy is that, in normal cases, the visits should become gradually more frequent as pregnancy advances, starting with monthly check-ups to week 28, followed by visits at two-weekly intervals up to week 36, and weekly visits thereafter. The basic content of care at each visit has not changed substantially over the years, although modern technology has led to the introduction of several new elements in pregnancy surveillance, the typical examples being Doppler echocardiography, sonographic imaging of the uterus and its contents, and biochemical and cell culturing techniques for the identification of abnormal fetuses or threatened by malnourishment.

In countries where women traditionally or on advice attend the antenatal services early in pregnancy, the average actual number of visits is ten to twelve, and attendance rates are nearly 100% (WHO, 1989). In the European Economical Community countries, Luxemburg is an exception with an average of only five visits, while its neighbour, the Netherlands, has between 12 to 14 (Blondel, 1986). A recent survey in Scotland revealed that the average number of antenatal visits for women with low risk pregnancies was 14 (Howie et al., 1991). In Sweden, the recommended number is 16 (Kamper-Jorgensen et al., 1986) and in Finland even women make 15.2 antenatal visits of which 2.2 visits were to a hospital clinic (Gissler, 1994). For the USA, providers including midwives, tend to exceed the American College of Obstetricians and Gynecology's guideline for the recommended number of prenatal visits (Baldwin, 1994).

In spite of the similarity of antenatal care programmes, surveys reveal that both the quantity and the quality vary. Services are, in theory, available to all pregnant women, either through private health care or through public programmes. Social inequality has been demonstrated in England and Wales, and in France, for late attendance and number of antenatal care visits (Garcia et al., 1989). In the USA, there are several barriers to utilization of services by women with low socio-economic status (Buekens, 1990).

Considerable resources are spent on antenatal care in industrialized countries, including the widespread use of medications during pregnancy. Recent reports demonstrate that up to 70% of low risk patients used medications other than iron supplements (de Jong, 1991; Rodriguez-Pinilla, 1992).

With regard to perinatal and neonatal mortality, it has been shown that better outcomes are associated with higher numbers of antenatal care visits per mother (Ryan, 1980). These concurrent trends have been used as arguments to justify expanding programmes without regard to the fact that in general, lower risk women are more likely to seek care earlier. The general belief of obstetricians is exemplified in this opening sentence of an article: "It is now universally accepted that antenatal care is probably the most important factor which determines the outcome of pregnancy" (Nylader & Adekunle, 1990). Although this may be true for very high risk women, parallel or opposing trends in time do not, in themselves, imply a causal relationship for the overall population. This particular claim has never been evaluated scientifically.

In recent years, voices have been raised to redefine the quality of care, instead of increasing quantity (Bryce, 1990; Elbourne et al., 1989). The screening ability of several obstetric procedures for the diagnosis of small-for-gestational age showed to be remarkably low (Backe, 1993). In 1992, funds were granted in Scotland to compare alternative models of antenatal care delivery (Greater Glasgow Health Board, 1991). In the Netherlands, van Roosmalen & Gravenhorst (1992) have proposed a controlled trial to test the effect of fewer visits in a low risk population. The key issue is not more or less antenatal care or reducing the number of visits, but implementing only those activities proven to be effective; the frequency and timing of visits can then be planned accordingly.

The situation is obviously different between developed and developing countries. In the later, conditions vary greatly regarding both quality and quantity of care, and improvement of services ought to be a matter of high priority. With the deplorably high maternal (AbouZahr & Royston, 1991) and perinatal mortality and morbidity (Weekly Epidemiological Record, 1989) prevailing in many of the poorest countries and regions of the world, any improvement would be expected to have a significant impact.

According to the World Health Organization (1989), there is wide variation in the proportion of women who receive antenatal care, both between and within geographic areas. In Africa the figures ranged from 2% to 99% and in Asia from 8% to 98%. Surveys covering the years 1986 to 1989 from a number of developing countries revealed figures for antenatal coverage mainly ranging from 50% to 90% (Buekens, 1990; ICMP, 1991). Analyses demonstrated that in most of these countries, the more care provided, the better the perinatal conditions. While social and cultural constraints may be an obstacle to attendance in some instances, the major reason for non-attendance is lack of resources (skilled personnel and money) and quality of care (Sundari, 1992) on the part of care-providing authorities, and lack of money among care-receivers. In urban areas, there are usually several levels of antenatal care provision. Regardless of level, each programme is aimed at following the traditional pattern. Still, many women are seen only once or a few times before they go into labour. In many developing countries where services are available, the smaller average number of visits is largely due to late initiation of antenatal care rather than non-adherence to the recommended standards (Nylander & Adekunle, 1990).

Recent attempts were made to evaluate antenatal care proposals for low risk women (Chan, 1993; Gissler, 1994; Raine, 1994; Kogan, 1994; Munjanja et al., 1996; Sikorski et al., 1996). Only in two trials (Munjanja, 1996; Sikorski, 1996) were there a clinically significant reduction in the median number of visits. A trial from Zimbabwe (Munjanja et al., also suggests a reduction in the incidence of preterm delivery. A trial from the U.K. (Sikorski et al., 1996) demonstrates that a moderate reduction in the number of visits is not associated with an increase in any of the negative maternal or perinatal outcomes, but more women in the intervention group were less satisfied with the reduced number of visits

schedule. There have been six randomized trials evaluating the effect of enhanced prenatal care by relatively broad-based interventions as compared with standard care on birth weight. This expanded antenatal care includes strong psychosocial support and educational activities at the clinics or in home visits. Four of these studies, with a total sample of close to 7,000 women conducted in different countries, showed no demonstrable effect on birth weight or gestational age (Spencer et al., 1989; Heins et al., 1990; Bryce, 1991; Villar et al., 1992). It should be noted, however, that in the Heins et al study, nurse midwives were able to care for high risk populations as compared with highly trained obstetricians, without differences in the outcome variables. The other two, although reporting no overall effect on birth weight and the rate of low birth weight (McLaughlin et al., 1992; Olds et al., 1986), demonstrated a small positive effect in a subgroup analysis. In the Olds study, an improvement in birth weight was observed among 21 teenagers, as compared with eleven "comparable" control mothers. In the stratified analysis of 86 primiparous mothers assigned to the comprehensive programme, an increase of 144 gm was seen (McLaughlin et al., 1992). No effect was present among multiparae. The results of these small stratified analyses are not corroborated by a larger multi-centre study (Villar et al., 1992).

Overall, there were 10 studies that provided data on preterm delivery and 11 that included LBW and type of delivery as outcome variables. The meta-analysis of these studies yielded odds ratios of 0.93 (95% CI 0.82 to 1.05) for preterm delivery, 0.93 (95% CI 0.81 to 1.07) for LBW and 0.96 (95% CI 0.86 to 1.07) for forceps delivery or cesarean section.

Furthermore, two recent randomized controlled trials evaluating preterm delivery prevention programmes that included weekly or bi-weekly visits, cervical examinations and education with a total sample size close to 3,300 women did not demonstrate a protective effect for preterm delivery or LBW (Goldenberg, 1990; Collaborative Group, 1993).

Conversely, it has been suggested that simpler, "less technologically-oriented" prenatal care would be less demanding to women and the health system, without compromising pregnancy outcome. There have been three attempts to evaluate a simplified system

(Zimbabwe, Holland, and Scotland). A model being tested in Scotland (Greater Glasgow Health Board, 1991), approaches this goal by proposing "only seven visits for those in the lowest risk category, with more emphasis on "psychosocial midwifery care".

By means of a randomized controlled trial, WHO, in collaboration with research institutions in 4 developing countries, proposes to evaluate whether a programme of antenatal care which emphasizes essential elements of care that have been demonstrated to affect pregnancy outcome is more effective than a traditional programme of antenatal care in preventing maternal and fetal morbidity and mortality. The 4 study sites include Rosario, Argentina, Havana, Cuba, Jeddha, Saudi Arabia and Khon Kaen, Thailand. The relative cost of the two programmes, health care providers' and patients' satisfaction will also be assessed by the other 2 components of the study.

The trial includes random allocation of antenatal care clinics in each of the 4 sites to either a traditional programme of care (i.e. the one currently in place) or to a rationally designed programme focusing on the essential elements of proven efficacy. Women attending either programme of prenatal care will receive their intrapartum care in hospitals.

3. OBJECTIVES

3.1 Goal

The goal of the whole project is to define and evaluate a new model of antenatal care that includes only those components which have been demonstrated to be effective in improving maternal and perinatal outcomes. The choice of each process and outcome variable is therefore made on the assumption that antenatal care will causally affect it.

3.2 Objectives

The objectives of the whole project are :

- To conduct a multicentre, multinational controlled trial comparing two models of antenatal care;
- To establish the relative merits of each model;
- To test whether the proposed new model is more effective than the traditional multivisit model with regard to maternal morbidity and perinatal morbidity and mortality, cost and satisfaction.

The objective of the study at Khon Kaen, Thailand is to participate in the high quality multicentre, multinational randomized controlled trial comparing two models of antenatal care. It was expected to contribute about 6,000 subjects for the whole project.

4. METHODOLOGY

4.1 Introduction

To test the hypothesis that a new model of antenatal care is more efficient than the traditional package with regard to specified maternal and perinatal end points, large numbers of pregnant women must be recruited and the study must include several physicians, midwives and other health care personnel, and have a multicentre design. Compliance with the assigned programme by care providers and receivers is crucial to implementation of the trial.

4.2 Study Design

A randomized controlled trial is necessary for the evaluation of the effect of antenatal care on pregnancy outcome specifically to control for bias in patient selection, as has occurred in most of the observational studies. Women delivering preterm infants have less "gestational time" for more prenatal visits, thus making the association between prenatal care and prematurity stronger. Conversely, late initiators of prenatal care have fewer preterm newborns because they are still pregnant after 36 weeks, thereby weakening the effect. Women with known medical complications tend to attend early and have more visits but also have more preterm/IUGR infants, producing the U-shaped curve of the association (more care, more preterm/IUGR). Finally, healthy well-educated women who have very low risk for preterm-IUGR will also attend early, have many visits and make the association stronger. All these recognized selection biases, as well as those presently ignored, can only be controlled by a large randomized controlled study design.

The study is a large, multiclinic, multisite, randomized controlled trial of two different models of antenatal care; a new model of care will be compared with the traditional recommended model as it is presently implemented in the selected sites. Maternal, fetal, perinatal, cost and satisfaction end-points will be compared. The trial are conducted in four sites worldwide; each study site will include between ten and twelve antenatal care clinics

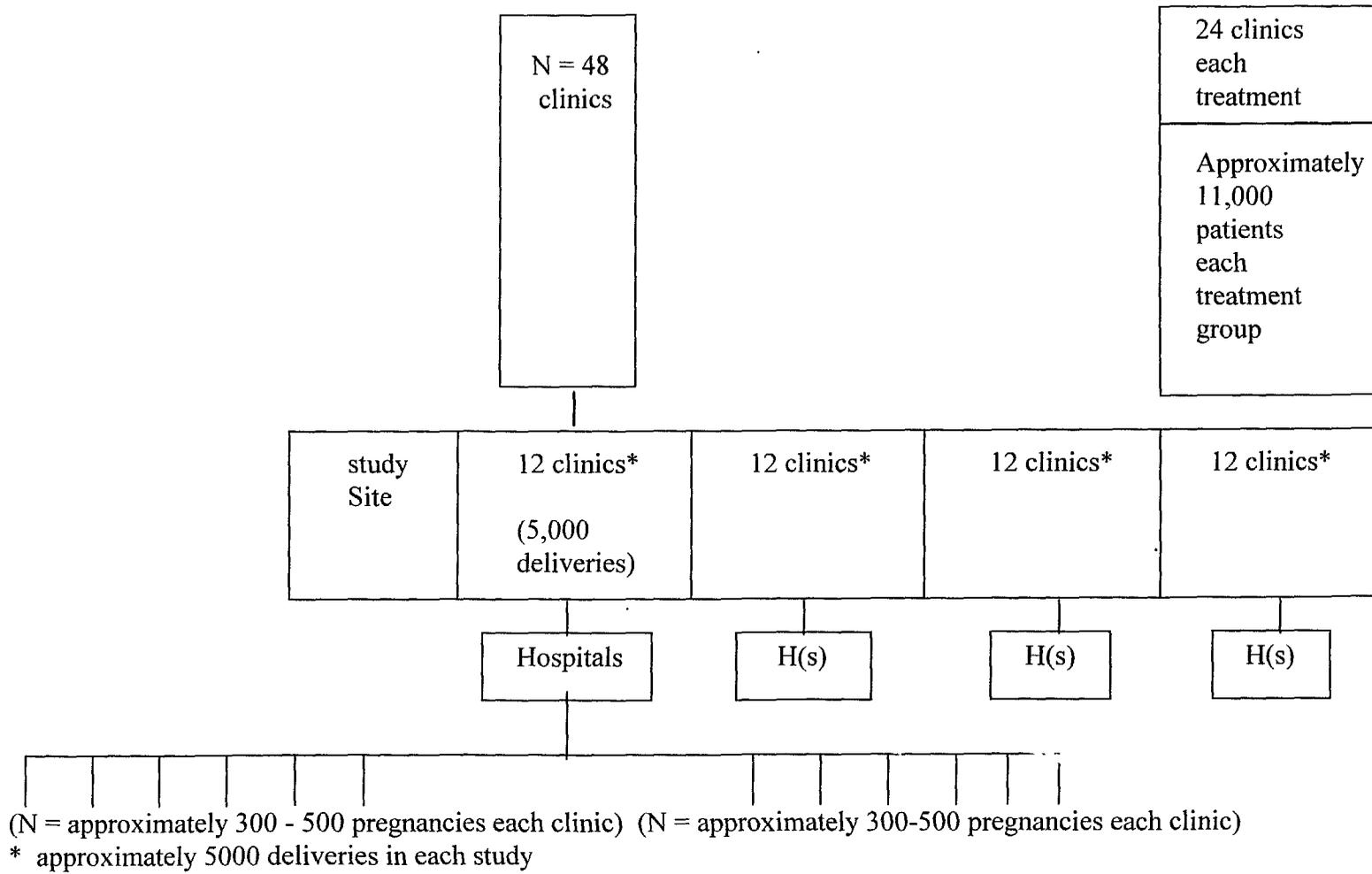
(clusters). All women attending each clinic will be included in the assessment of the clinic end-points and will be registered on their first antenatal visit and followed until discharge from the hospital post-partum. Deliveries from all ANC clinics (intervention and control) in a particular study site should occur at the selected medical facilities (Figure 1). Antenatal care clinics (cluster randomization), not individual women, will be randomized to the two arms of the study. Randomization will be stratified within each geographic study site by the size of the patient population enrolled in each clinic or cluster (large, medium and small clusters).

4.2.1 Randomized controlled trial

When testing the effect of new drugs or procedures by comparing against old treatment or placebo, patients are usually individually randomly allocated to one or the other alternative treatment modality. Statistical comparison is then made between patients allocated to each of the two (or more) treatment groups. In this design, precautions are taken to avoid bias favoring one or the other treatment, and against the possibility that care providers and test subjects, consciously or unconsciously, violate procedural rules in order to affect the outcome. This is often achieved by "blinding" the study patients and in some instances also the researcher ("double-blinding").

Obviously, the two models of antenatal care cannot be "blinded." Given prior information, it will immediately be clear to participants (both care providers and care receivers) to which arm of the trial each belongs. It is also obvious that care providers, as a condition for participation, must be given full information about both antenatal care programmes before randomization. Ideally, the two models of antenatal care should be tested by random allocation of study subjects, which would require detailed information before consent is given. Full information with free choice of participation implies that those not willing to participate will receive an alternative form of care, which may be the traditional, the new model or even a combination of the two. This invites new problems which would invalidate the trial.

Figure 1: Trial Organization



Within the individual study site, there would also be confusion regarding the content of each visit of the individual woman, and there would be the obvious risk that the two systems may ultimately fuse into one ("contamination") before the trial is completed (Kramer, 1989). To avoid these problems, which would, in the end, invalidate the trial, we propose to randomize by unit (cluster randomization). The ethical questions this raises will be discussed in Section 4.15.

4.2.2 Randomization by unit

The study units will be antenatal care clinics serving well-defined geographic areas. Randomization by unit (or clusters) is an excellent methodological strategy in evaluating the effect of global changes in mode of practice. Detailed review of the properties and limitations of design have been published elsewhere (Donner and Klar, 1994; Buch and Donner, 1982). For example, a very important large randomized trial of vitamin A supplementation conducted in northern Ghana using geographical areas as randomization units (clusters), was recently completed and published (Ghana VAST Study Team, 1993). Cluster randomization has also been used for the evaluation of a community intervention of growth monitoring in South India, in which six pairs of villages were formed and randomization was conducted within them (George, 1993).

These recent examples, along with previous large studies also using cluster (clinics or health care providers) randomization in the perinatal field (Grant, 1989; Bullough, 1989), strongly support the usefulness of this type of study design for the evaluation of health care strategies.

In the case of the present study the two main reasons for choosing clusters as units of randomization are: to reduce treatment contamination and for administrative and logistic convenience in the implementation of the intervention. As it is possible that analyses using women as units may be performed, we have accounted for the between cluster variation in the calculation of sample size and study power.

The population attending the clinics in each country should be similar with regard to sociodemographic factors, and have study-relevant mortality and morbidity rates in the same order of magnitude. An antenatal care programme following traditional standards delivered through the public sector should be already available to pregnant women. Furthermore, all participants should plan to deliver in hospitals, not least for practical recording purposes. To obtain a reliable answer within a reasonable period of time, there will be several antenatal care clinics (clusters) for comparison, stratified by study site and cluster size. Each clinic or cluster will be expected to manage between 450 and 500 antenatal care patients during the study period. However, as it is more important the number of clusters than the size of them it is possible that for logistic reasons smaller antenatal care clusters could be accepted (about 300 antenatal care patients per cluster).

Each site considered for the study should be able to:

1. produce reliable data on the primary maternal and newborn outcomes in the city or region.
2. Provide written evidence that the new programme will be acceptable to local authorities and physicians.
3. Recruit between 10 and 12 antenatal clinics from the public sector (see criteria for clinic selection) in a geographically identified region.
4. Have a common formal system of perinatal data collection and maternal cards already in place.
5. Have an effective system for referral of high-risk women from the clinics to a tertiary level hospital.

6. Have a regional epidemiological research unit with field research experience; previous participation of this unit in multicentre studies is required. Computer facilities at the research unit-hospital or university-should be available to the study group.
7. Country should allow data (multicentre trial) to be sent to the central analysis centre (Geneva) and to be pooled with those from the other centres.

The criteria for each antenatal care clinic to be included for randomization is as follows :

1. Each antenatal care clinic (the randomization unit) to be included should be able to provide between 300 and 500 new patients in a period not longer than 18 months.
2. Intervention and control clinics will be in the same geographical area.
3. "Same geographical area" relates to same city or district; the ideal situation will be clinics serving different neighbourhoods of a city or areas of a rural province.
4. All women from these antenatal care clinics should deliver at hospitals.
5. The hospitals should also be the referral place for all high-risk patients.
6. The clinics should be part of a public (or semi-public) antenatal care system. Military hospitals or social security institutions are also eligible. The study will not include clinics where direct fee-for-services payments are required.
7. All clinics should have an antenatal care system already in place with norms and predefined activities which are followed.

8. The clinics should be able to implement new simple tests or activities as required by the protocol. Funds for these new activities should be provided by the institution(s), as they will be for direct patient care only. These few new activities will replace several presently implemented ones.
9. The clinics should have an already working and economically supported minimum staff required for patient care by the protocol.

4.2.3 Limitations of the study design

It is possible that the outcome of women attending the new programme will be altered by the introduction of a new system, regardless of its components and of any differential effects of the two treatments. Furthermore, it is also possible that outcomes will improve in the control group by means of a better utilization of resources available in the traditional system, as well as by more active participation of nurses and physicians. Patients entered into a trial tend to receive more careful management in all aspects of care. Finally, although effort will be made to maintain a blind status for delivery and neonatal care providers, it is likely that they will know the treatment status and perhaps act differently based on their belief of antenatal care. However, most of the selected outcomes are little influenced by intrapartum care and it is expected that this effect will be minimum. Nevertheless, the study will attempt to evaluate this effect, if present, by the following mechanisms:

1. During the preparatory phase of the study, information were collected at the cluster level in all sites on the main outcome variables and a selected number of process variables. This baseline information will be compared with data obtained during the trial (before and after analysis). Most likely, available baseline information will be at hospital or area level, and specific clinic data will be obtained during the preparatory phase only.

2. Information on intrapartum events partially unrelated to antepartum care, e.g. emergency cesarean section, forceps delivery, were collected during the preparatory phase. Comparisons will be made between the two treatment groups; it is expected that no differences will be present during the preparatory and study periods.
3. Trends will be observed in perinatal events at all participating hospitals irrespective of whether patients are participating in the antenatal care study.

4.2.4 Discontinuation of study units or patients

The complete study will be discontinued or stopped as decided by the Data and Safety Monitoring Committee and the Steering Committee if the "experimental group" is having overall a worse outcome, as defined in the "Stopping Rules". Based on sample size calculations, an increase in the intervention group, of more than 25% from the control group in any of the primary outcomes will be specifically analysed by the Data and Safety Monitoring Committee.

Discontinuation of a study cluster is an important problem and steps will be taken to reduce the likelihood of this before the initiation of the study. There are two elements that can contribute to the need for discontinuation:

- (a) very low recruitment rate (< 30% of the expected number of patients in a clinic/s).
- (b) lack of compliance in the application of the new antenatal care programme by clinic personnel after initial acceptance.

To prevent the first problem, a retrospective review of several years' trend in patient attendance at the clinic was studied. Only those clinics with stable and adequate number of patients initiating antenatal care are included. To prevent the second problem, meetings were

conducted with the staff of all clinics to evaluate their willingness to participate in the trial if they are randomized to the intervention group, and a "dry run" of the trial was conducted after the preparatory workshops for a period of one month in some of the clinics allocated to the new programme in order to detect problems and reaction of personnel. Only after this period, and upon general agreement with the intervention, would the new programme be considered ready to start.

During the course of the study, and only under extreme circumstances (it could lead to major bias), the following criteria could be used for discontinuation of a study unit:

Lack of adherence to data collection principles;

- major organization changes which make continuation impossible;
- rate of recruitment less than 30% goal for at least 6 months;
- more than 20% of eligible patients refuse to participate in the study and choose other clinics.

Any excluded clinic/s (cluster/s) will be included in the final analysis in the group to which it was randomized up to the time of the discontinuation, regardless of the completeness of the programme implemented. All women included up to discontinuation will be followed up until delivery and included in the analysis.

Patients will not be discontinued from the new antenatal programme. If some women refuse to continue, they will be offered the traditional antenatal care at the same clinic or referred to an alternative clinic if it is located nearby and does not represent any inconvenience for the patient. In both situations, patients will be included in the analyses as part of the cluster where they were originally enrolled.

4.2.5 Eligibility of patients

All patients attending the first prenatal visit at the study clusters after the date of the start of the study, regardless of their history or medical condition, will be included in the study, and their medical record will be used in the analyses. Those enrolled for prenatal care at the control clinics will follow the standard procedure and be referred for delivery at the identified hospitals. Women enrolled in the new (intervention) programme clinics receive the new prenatal care programme and/or standard treatments of medical care if needed at any time during pregnancy. All patients will be considered for the analysis as part of the intervention population.

If a women has more than one pregnancy during the study period in one of the antenatal care clinics of the study, only the first pregnancy of that women will be included in the analysis.

Efforts will be made to locate those women who registered for antenatal care but had an abortion. Those women for whom information is not available for pregnancy outcome or termination will be treated as lost to follow-up.

4.3 The study site at Khon Kaen, Thailand

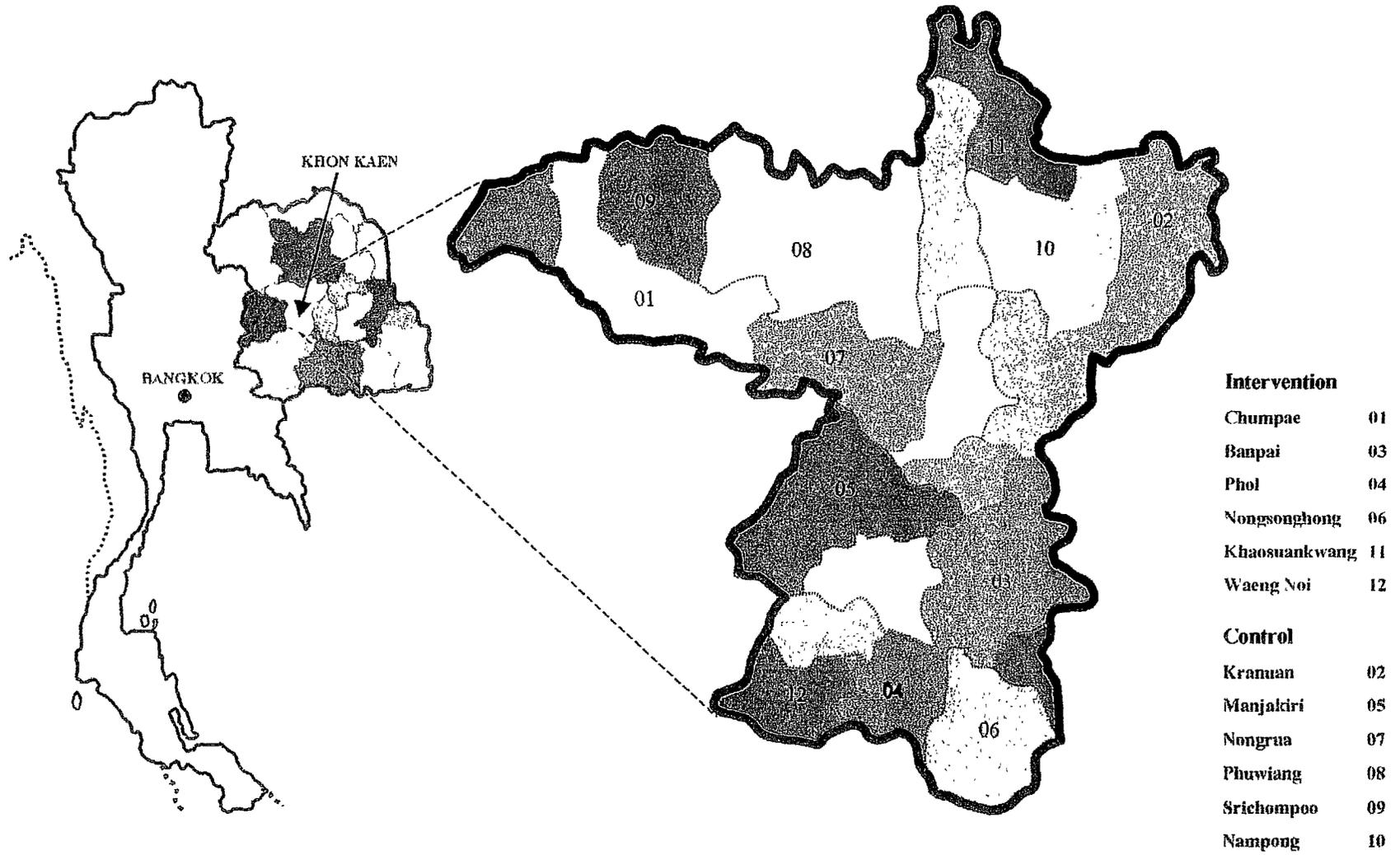
Khon Kaen is a province in northeast Thailand, 450 kilometers from Bangkok. The total area of the province is 10, 145 sq. km. The population in 1993 was 1.7 million with a growth rate of 1.1%. There are 20 districts which are divided into 1939 villages. The main incomes of the province are from agricultural products.

Concerning the health care services in Khon Kaen, the ministry of public Health (MOPH) has the following health care facilities:

1. 1 provincial health office
2. 1 regional hospital (638 beds)

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3. 4 60-bed community hospitals
4. 6 30-bed community hospitals
5. 10 10-bed community hospitals
6. 20 district health offices
7. 193 health centers

Khon Kaen can be considered as the center of the Northern part of Northeast Thailand. It has many government health institutions e.g. Khon Kaen University (Srinagarind) Hospital, Health Promotion Center, Medical Science Center, Communicable Disease Control Center etc.

With regard to maternal and child health (MCH) care, Khon Kaen University, Health Promotion Center serve as the academic support institutes. The Provincial Health Office makes the policy. MCH care is available at all levels of health care facilities from regional hospital down to health center.

An antenatal care (ANC) service is also available at all levels of health care facilities, the majority of which occurs at community hospitals. About 90% of women delivery their baby at the health care facility where they have had their antenatal care. Eighty to ninety percent of deliveries take place in health care facilities.

The ANC scheme follows the traditional western recommendation. Pregnant women are scheduled to come to the ANC clinic once a month during the first 7 months of pregnancy, every 2 weeks during the 8th month and every week in the final month.

In the community hospital, nurses provide ANC for uncomplicated pregnant women. Pregnant women with complications are managed by medical officers or referred to regional or university hospitals if necessary. Laboratory tests including hematocrit and serology test for syphilis (usually VDRL) are routinely performed. Two doses of tetanus toxoid are also given to every pregnant woman during the antenatal period.

Uncomplicated deliveries are attended and conducted by nurses. Complicated deliveries are managed by medical officers or referred to higher level of care as appropriate. Facilities for cesarean section are available in all 3 sixty-bed and 6 thirty-bed community hospitals and some ten-bed hospitals.

Nurses from the community hospitals and midwives from the health centres make a home visit for postpartum women in their respective areas. Health education and management of postpartum complications are provided as appropriate.

The name of the clinics (clusters) and their expected number of new antenatal care patients per year and low birth weight rate is shown in Table 1.

Table 1 : Antenatal Care Clinics (Clusters) included in the study

Stratum	Clinic Number	No. of new Antenatal Care patients/year	LBW rate
Thailand (large)			
Chumpae	01	1330	8.0
Kranuan	02	1025	10.0
Thailand (medium)			
Banphai	03	669	5.6
Phol	04	469	9.1
Manjakiri	05	466	11.3
Nongsonghong	06	464	9.4
Nongrua	07	451	5.6
Phuwiang	08	445	5.6
Thailand (small)			
Srichompoo	09	293	6.7
Nampong	10	268	7.9
Khaosuankwang	11	250	8.0
Waeng Noi	12	204	4.4

4.4 The intervention

The trial will be a direct comparison of two programmes of antenatal care. One is the standard antenatal care presently offered in the selected sites with follow the traditional western recommended care. The other programme includes scientifically evaluated, objective-oriented activities.

4.4.1 Introduction

Antenatal care is to a large extent targeted towards primary and secondary prevention of diseases and pathological conditions during pregnancy and delivery. It had four main components:

- (1) identifying women with current health conditions likely to jeopardize the outcome of pregnancy (e.g. chronic hypertension, diabetes, malnutrition);
- (2) identifying currently healthy women at increased risk of health conditions likely to jeopardize the outcome of pregnancy (e.g. very young women, women with poor obstetrical history);
- (3) early detection and treatment of health conditions likely to jeopardize the outcome of pregnancy (e.g. preeclampsia, anemia, urinary tract infection);
- (4) sensitizing pregnant women and their families to health conditions likely to jeopardize the outcome of pregnancy and ensuring an appropriate response from them (smoking, STDs, preterm labour, hemorrhage).

Activities to be included in the new programme are within three general areas:

- (a) screening actions for health conditions likely to increase the risk of specific adverse outcomes of pregnancy;

- (b) therapeutic interventions known to affect these outcomes beneficially;
- (c) sensitizing pregnant women to potential health problems and explaining appropriate responses.

As with any other screening tests, those included in the programme should conform to the common criteria for screening of disease (Cadman et al., 1984). However, screening for new medical risk in antenatal care is a continuing activity, and the timing of the screening is influenced by the specific condition under consideration. Thus, formal numerical risk-scoring, traditionally used in obstetric clinics, is not included because of its low sensitivity and specificity (Kestler, 1991; Alexander & Keirse, 1989), and the lack of evidence of the effectiveness of such risk-scores obtained from randomized controlled trials (Alexander & Keirse, 1989).

Therapeutic interventions known to have a positive effect on pregnancy outcomes were selected from current practice, extensive literature review and recently published meta-analyses (Oxford Database, Rooney, 1991; National Academy of Sciences Antenatal Care Review). These interventions are related to specific process and impact indicators are presented in Table 2.

The activities to be included in the antenatal visits were selected using these mechanisms, and the final number of visits and their components were then determined. Thus, the number of visits are based on the need to perform an activity rather than on a fixed (few or many) a priori number.

Table 2 : THE RELATIONSHIP BETWEEN ANTENATAL INTERVENTIONS AND OUTCOMES (a)

INTERVENTION	IMPACT			INDICATOR	
	IMMEDIATE	INTERMEDIATE	DELAYED	PROCESS	IMPACT (compared with control group)
Tetanus toxoid	Increase maternal tetanus antibodies	---	Reduce neonatal & maternal tetanus	# complete doses given	Rate of neonatal cases; rate of maternal cases reduced
Treat syphilis	Treat maternal syphilis	Reduce congenital syphilis	Reduce stillbirth & neonatal deaths by syphilis	% women screened, % fully treated of those (1)	Rate of cases congenital syphilis avoided
Malaria treatment and prophylaxis	Maternal morbidity reduction	Increase Hb, reduce new episodes	Reduce SA, increase BW; reduce NND; reduce maternal death	% women took tablets; % women completed treatment	PNM rate; rate of malaria deaths, rate of IUGR
Folate supplementation	Increase Hb	Reduce infections; improve case-fatality from hemorrhage; increase BW	Reduce death from hemorrhage & from LBW	% women supplemented Hb at third visit; Hb at delivery	Rate of maternal deaths due to sepsis or hemorrhage; rate of LBW infants
Measure blood pressure	Early identification of women at risk of HDP; early diagnosis of chronic hypertension	Reduce preeclampsia, eclampsia/HDP	Reduce deaths from eclampsia; reduce LBW	% BP measured; % HDP detected & treated; % emergency admin. for HDP % eclampsia	Rate of women with fits; rate of perinatal mortality; rate of LBW
Health education	More women aware of symptoms of life-threatening conditions	Improve care seeking behavior, reduce emergencies, increase rate of smoking cessation	Reduce deaths, pregnancy complications	% delivery by level of care recommended; % of condition at admission	Rate of maternal & perinatal mortality, by cause
Referral for delivery	Reassurance to mother that intrapartum care will be provided at correct level	Increase tertiary hospital deliveries in HR women	Reduce perinatal deaths	% HR deliv. in tertiary hospital; % LR delivery in general hospital	Rate of maternal & perinatal mortality (subgroup analysis of HR mothers)

BW : birth weight
 LBW: low birth weight
 NND: neonatal death
 PNM: perinatal mortality

HDP: hypertensive diseases of pregnancy
 HR : high risk
 LR : low risk
 SA : spontaneous abortion

Table 2 : THE RELATIONSHIP BETWEEN ANTENATAL INTERVENTIONS AND OUTCOMES (b)

INTERVENTION	IMPACT			INDICATOR	
	IMMEDIATE	INTERMEDIATE	DELAYED	PROCESS	IMPACT
Classification of risk level, 1st visit (including clinical history)	Classification of women to receive care at clinic (new programme) or other level	Provide care according to health needs	Reduce perinatal/ maternal mortality	% false positive and false negatives of the screening method	Reduction in risk specific perinatal mortality
Continuous risk assessment (development of symptoms signs)	Identification of women with need for special care	Refer to adequate level of care	Reduce negative pregnancy outcomes related to these conditions	% women referred for the clinic; % women admitted in emergency services	Reduction of perinatal mortality related to these conditions
Maternal weight (follow-up visits)	Detection abnormal weight gain patterns; referral to nutrition clinics of low weight gain/underweight women	Improve maternal nutritional status; reduce IUGR	Reduce maternal depletion syndrome; maternal overweight	% women with abnormal weight gain patterns detected	Rate of reduction in IUGR; rate of reduction of women with very low weight post partum
Measure hemoglobin to all women at 30th week of pregnancy	Detection women in need of higher Fe doses; detection women with hemoconcentration	Improve maternal nutrition/ health status; increase placental circulation and reduce fetal growth retardation	Improve maternal nutritional status; reduce LBW/IUGR; reduce risk of maternal death related to hemorrhage	% high risk women detected with very low hemoglobin levels; % women with higher Fe doses	Rate of postpartum hemorrhage; rate of women needing blood transfusion; maternal mortality intrapartum/ postpartum
Antibody titration to mother of Rh(-); newborn hemolytic diseases (1st visit)	Refer to hospital	Treatment of Rh(-) fetal anemia	Reduce fetal death	% of referred women	Reduction fetal/neonatal mortality
Prophylaxis for Rhesus (30 weeks)	Post partum prevention	—	Reduce Rh(-) disease	% Rh(-) mother with γ globulin postpartum	
Correction of breech presentation at term & external version	Reduce breech delivery; Reduce C.S. for breech presentation; reduce overall C.S. rate	Reduce perinatal mortality for undetected breech vaginal deliveries	Reduce need for repeated cesarean section	% breech presentation at onset of labor	Rate of C.S. for breech presentation; rate of perinatal mortality reduced related to breech vaginal deliveries

Table 2 : THE RELATIONSHIP BETWEEN ANTENATAL INTERVENTIONS AND OUTCOMES (c)

INTERVENTION	IMPACT			INDICATOR	
	IMMEDIATE	INTERMEDIATE	DELAYED	PROCESS	IMPACT
Measure maternal weight/height (1st visit)	Detection of underweight mothers	Increase weight gain during pregnancy; improve fetal growth	Reduce risk for maternal depletion syndrome	% underweight mothers detected; % underweight women referred to nutrition clinic	Rate of LBW and IUGR; reduction of PNM
Clinical symptoms of severe anemia	Select women for Hb detection before 30th week	Initiation of higher Fe dose to women with low Hb values	Reduce risk of severe anemia during pregnancy	% women with high Fe dose; % anemic women detected by Hb values <30th week	Rate of anemic women prepartum & postpartum
Measure hemoglobin for high risk women for anemia (1st visit)	Detect women for higher Fe doses; confirm clinical diagnosis	Improve maternal morbidity/ health status; improve fetal oxygenation	Improve maternal nutrition status; reduce LBW/ IUGR; reduce risk of maternal death related to hemorrhage	% of high risk women detected with very low hemoglobin; % women with high Fe dose	Rate of post-partum hemorrhage and of women needing blood transfusion
Urine dipstick to detect protein in 1st visit & subsequent visits	Identification of preeclamptic women; referral to hospital; identification of women with renal disease	Reduce incidence of severe preeclampsia	Prevent eclampsia, IUGR, maternal mortality	Admission to hospital for severe preeclampsia; referral of cases versus urgent admissions	Rate of severe preeclampsia/ eclampsia ; perinatal mortality & morbidity
Urine multiple dipstick in 1st visit	Identification of women with asymptomatic bacteriuria	Reduce incidence of overt infection or pyelonephritis	Prevent chronic renal disease, preterm delivery	% of women treated from those with positive cultures	Incidence of pyelonephritis & preterm labor & LBW
Pregnancy test (1st trimester, no clinical evidence of preg.)	Reassurance of pregnancy; provide information for possible abortion		Reduce unwanted pregnancies		
Assessment of uterine size	Identification of IUGR fetuses; multiple pregnancies	Referral to high risk clinic; timely delivery of IUGR	Prevent complications of IUGR in neonatal & post-natal period	Referral of IUGR for induction/elective C.S.	Rate of fetal death, IUGR in NICU; emergency C.S. in IUGR for fetal distress

BW : birth weight

HDP: hypertensive diseases of pregnancy

NND: neonatal death

LBW: low birth weight

HR : high risk; LR: low risk

PNM: perinatal mortality

4.4.2 The new antenatal care programme

Introduction

The new package is a consequence of these deliberations. Furthermore, it will be based on the following principles:

- (a) A programme which differentiates between low and high risk cases should have a simple set of valid rules to be followed.
- (b) Designation of high risk should be given with prudence, and the refer of high risk cases to higher level of care done only when the higher level care provision can reduce the risk or alter the outcome.
- (c) Women will be considered and made to feel that they are the centre of the activities. They will be seen by appointments strictly kept by staff to reduce mothers' waiting time, and additional activities and tests will be carried out the same day. On the other hand, no patient requesting interim care at the clinic will be refused, and the clinics will offer prenatal consultation for as many hours as possible. It has been shown that the greater the number of clinic hours, the more prenatal care is sought (Lewit, 1983).
- (d) Only examinations and test which serve an immediate purpose and are of proven beneficial are included. If there is justification for performing a test only once during the pregnancy, it is performed at the most appropriate time, that is, when an abnormal test result requires intervention.
- (e) At the cost of some sensitivity and specificity, simple and easy-to perform tests have been chosen, and tests which give rapid results. Wherever possible, the tests should be performed at the antenatal clinic or in its immediate vicinity.

Most of the new package could be implemented by health care workers at and below physician level, e.g. formally trained midwives and nurses, because only a few elements require a physician's qualifications for interpretation. This, of course, does not exclude the active participation of doctors in medical supervisory responsibility. However, we would like to emphasize that the new package only includes elements proven to be effective and that it is not a transfer process of "outdated rituals" from doctors to midwives (Steer, 1993).

The basic components of the new programme are throughout four antenatal visits. Health workers at the intervention clinics will have the "Manual of Clinical Activities" which presents in detail the activities to be carried out. The description of these visits are presented as follows:

The First Visit

The first visit should occur ideally in the first trimester, around the 12th week of pregnancy. However, all pregnant women initiating prenatal care in the intervention clinics regardless of their gestational age will be examined following the norms for the first visit and enrolled in prenatal care at that time. The first visit examination is expected to take 30-40 minutes. Emphasis is placed on the medical and obstetric history. Objective findings at examination give additional or confirmatory evidence. While the case history, proposed conforms to and even exceeds traditional standards, the elements of the physical and biochemical examinations are fewer and less resource-demanding than those commonly used.

Pregnancy tests are widely used and abused by the health system and women. In the U.K. it is reported that up to seven pregnancy tests are performed for each live birth (Voss, 1992). Pregnancy tests will be provided at the clinic to women during the first trimester and results given to women who request reassurance that they are pregnant if there are no signs or symptoms of pregnancy. In countries where abortion is legal, women may request a pregnancy test if they are planning an abortion and do not trust a negative clinical judgement.

Social, educational and work components help to identify risk. Work may be physically hard, and it may give exposure to teratogenic agents (heavy metals, toxic chemicals, ionizing radiation). Women could be advised and provided with the required documentation to reduce work if it is very hard or it requires long standing positions (Launer et al., 1990). The feasibility of classifying women by social class indicators and providing additional family support to very poor women could be considered at some study sites, as the hard work/negative pregnancy outcome relationship appears to be related to social class (Klebanoff et al., 1991; Barnes et al., 1991).

Only one routine vaginal examination during pregnancy is recommended, including taking a sample for Pap smear if this is routinely performed in the clinics and screening for symptomatic STDs (Wangford & Smaill, 1989). It could be postponed until the second visit if the doctor or midwife feels that the women or her companion would not accept this. In women with (a history of) bleeding in the present pregnancy, vaginal examination should not be performed at the clinic after the first trimester, and the patient should be referred for ultrasonography examination, if available at the hospital, to exclude placenta previa (Chamberlain, 1992).

As routine iron supplementation will be given to all women, hemoglobin would be determined only at 32 weeks (the third visit) unless there are clinical signs of anemia.

Easy access to care in case of need is essential in the new package. This must be guaranteed through written information about which place and which person to contact, with telephone numbers if available, on a 24-hour basis.

Individual instruction is an essential element of antenatal care. Sufficient time must be set aside for communication and planning, especially at the first visit. We anticipate more available time for each individual visit as a result of the lower number of visits for low risk (the majority of) women, in addition to shorter waiting times and immediate medical availability for unscheduled visits. It will include general information about pregnancy and delivery and individual counselling if demanded or deemed necessary. Otherwise, patients can

go home sooner. The individual counselling will be specific to each woman's condition and emphasis will be on listening to her problems. It should include simple written instructions in the local language, even to illiterate mothers (often family members or neighbors can read). This activity will be focused on instruction for actions to be taken in case of pregnancy-related emergencies. Less emphasis will be placed on formal social support or general health education, as several randomized controlled trials have failed to demonstrate major benefits (Oakley, 1990; Villar et al., 1992).

Risk assessment for antenatal complications is strictly adhered to. However, less emphasis will be placed on screening for place of delivery given the recognized unpredictability of screening women early in pregnancy for intrapartum complications (Hundley, 1994). The large majority, low risk women, are expected to follow the new model of antenatal care. More frequent checks at primary care level are preferred for specific treatment or test follow-up, rather than referral to hospitals. The decision on which women will follow the basic component of the Antenatal Care Package is made by using "Classifying" form.

Content of the first visit:

I. Personal information

- I.A. Personal: Name, age (date of birth), address (telephone no.), marital status.
- I.B. Social: Housing: type, size, no. of occupants. Sanitary conditions: type of toilet, source of water, electricity, cooking facilities.
- I.C. Education: Literate? Completed year of school (educations level: primary, secondary, university).
- I.D. Work, economy: employed (salaried work), type of work and position. Own/husband's.

II. Medical history

- II.A. Specific diseases and conditions: tuberculosis, heart disease, chronic renal disease, epilepsy, diabetes mellitus. Venereal diseases. HIV status, if known. Other specific conditions depending on prevalence in study site (for example, hepatitis, malaria, sickle cell trait).
- II.B. Other diseases, past or chronic. Operations other than cesarean section. Blood transfusions. Rhesus (D) antibodies. Allergy.
- II.C. Current use of medicines.
- II.D. Period(s) of infertility: when? – duration, cause(s).

III. Obstetric history

- III.A. Number of previous pregnancies: date (month, year) and outcome of each event (livebirth, stillbirth, abortion, ectopic, hydatidiform mole). Specify (validate) preterm birth, specify type of abortion, if possible. Birth weight (if known). Gender. Periods (how long?) of lactation.
- III.B. Special maternal complications and events in previous pregnancies (specify which pregnancy(-ies), validate by records (if possible):
 - recurrent early abortion
 - induced abortion complications
 - thrombosis, embolus
 - hypertension, preeclampsia, eclampsia
 - placental abruption
 - breech, transverse presentation
 - obstructed labour, including "dystocia"
 - operations

- cesarean section
- forceps, vacuum extraction
- manual/instrumental help in vaginal breech delivery
- manual removal of placenta
- third degree tears
- third stage excessive bleeding
- puerperal sepsis
- gestational diabetes

III.C. Special perinatal (fetal, newborn) complications and events in previous pregnancies (specify and validate as for III.B.):

- twins, higher order multiples
- low birth weight (LBW): < 2500 g, or to be defined
- intrauterine growth retardation (if feasible)
- rhesus-antibody affection (erythroblastosis, hydrops)
- malformed, chromosomally abnormal child
- macrosomia (> 4500 g) newborn
- resuscitation, other treatment of newborn
- perinatal, neonatal, infant death (also: later death).

IV. History of present pregnancy

- IV.A. Date of last menstrual period (LMP). Certainty of dates (by regularity and accuracy of recall, other relevant information).
- IV.B. Habits: smoking/chewing tobacco, alcohol, drugs (frequency, quantity).
- IV.C. Any untoward events (pain, vaginal bleeding of threatened miscarriage, hemorrhage).
- IV.D. History of malaria attacks.

V. Physical examination

- V.A. Weight and height; blood pressure (BP). Chest, heart auscultation, Symphysis to fundus distance (in centimeters). All women.
- V.B. Signs of severe anemia: complexion, fingernails, conjunctiva, oral mucosa, tip of tongue. Shortness of breath. All women.
- V.C. Consider vaginal examination, especially if untoward events are positive (IV.C)

VI. Special tests

- VI.A. Urine: protein, multiple dipstick for bacteriuria.
- VI.B. Blood: syphilis (rapid test) result while waiting in the clinic. If positive: treat.
Hb: only if signs of severe anemia.
Blood type and rhesus.

VII. Assessment and referral

- VII.A. Determine the expected date of delivery based on LMP and all other relevant information. Use 280-day rule (LMP + 280 days). Observe: same women will refer to the date of the first missed period when asked about LMP, which may lead to miscalculation of term by four weeks.
- VII.B. Risk assessment (advice: see IX): Women are classified as eligible for the basic components of the new antenatal package or in need of special care and to be followed at the clinic or hospital (Classifying form, Appendix I).

For the following conditions, if diagnosed, is recommended:

- diabetes: refer, must have continued higher level care
- heart disease: refer
- renal disease: refer
- epilepsy: advice on continued medication
- drug abuse: special care
- signs of severe anaemia and Hb < 70 g/dl: higher iron dose, or refer if shortness of breath
- HIV positive: counsel on risk to offspring; refer
- risk of genetic disease, and possibility of further checks: refer
- primigravida: hospital delivery
- previous stillbirth: refer
- previous growth-retarded fetus (validated IUGR): refer to higher level of care
- hospital admission for eclampsia/pre-eclampsia: refer
- previous cesarean section: stress hospital delivery
- high blood pressure (> 140/90 mmn Hg) refer for evaluation
- Body Mass Index (BMI) (Weight in Kg/height (m)²) (refer for nutritional evaluation if BMI < 18.5 or > 32.3 kg/m²).

Please note that the BMI cut off point < 18.5 is based on calculations of chronic energy deficiency in adults (James et al., 1988) that require validation against maternal and infant outcomes. This value unfortunately requires also local adaptation; for example the mean BMI in a sample of Guatemalan women (N = 12,786) was 22.5 + 3.14 kg/m² (Flegal K et al., 1993). It is possible that if a local weight for height reference chart is available it can be incorporated in the clinical procedures, as it has been shown that the use of body mass index does not represent an advantage over no power-type indexes (weight/height) (Flegal et al., 1993). If this is not the case, pre-pregnancy maternal weight (using local cut-off points) is recommended for evaluation of the nutritional status during the first antenatal visit.

- evidence of pre-eclampsia: refer to higher level of care, or hospitalize.
- suspicion of fetal growth retardation (symphysis-to-fundus distance too low): arrange extra visit at week 29.
- mother does not feel fetal movement: use hand-held doppler for detection of fetal heart sound. If negative, refer to hospital.

VIII. Intervention

- VIII.A. Iron: continue, all. If Hb (see VII.A.) < 70 g/l: higher dose, or if with symptoms, refer.
- VIII.B. If bacteriuria at first visit was treated and test still (+), refer.
- VIII.C. If bleeding, refer.

IX. Advice, questions & answers, and appointment

- IX.A. Repeat all advice given at first visit (A-E).
- IX.B. Questions & answers: time for free communication.
- IX.C. Advice on where and whom to call in case of emergency, as at first visit.
- IX.D. Appointment: third visit: at (close to) 32 weeks.

X. Record keeping

- X.A. Office record.
- X.B. Home based record.

The Third Visit

The third visit should take place around the 32nd week and is expected to take 20 minutes. The examinations and tests are restricted to measuring blood pressure, symphysis-to-fundus measurement, a urine test for primiparous and those with history of hypertension

preeclampsia and eclampsia, and hemoglobin on all. Special attention should be directed toward discovery of twins during the external abdominal examination and uterine height measurement.

Referrals are based on symptoms and findings which require special intervention. For example, high haemoglobin (> 130 g/l) in absence of other symptoms may mean poor fetal nutrition, warranting an extra visit at week 36 to evaluate fetal growth.

As some of the women will go into labour and deliver before the next scheduled visit, extra attention must be given to instructions and advice in the event labour starts (pains or leaking of amniotic fluid). Written instructions should reconfirm the advice, and plans for getting to hospital should be reviewed. The importance of a post-partum visit, including recommendations for lactation and conception, is stated to ensure that the women is seen at the clinic within the two months post-partum.

Content of the third visit:

I. Personal information

Note any changes or events since second visit.

II. Medical history

- II.A. Review relevant issues of medical history as recorded at first and second visits.
- II.B. Intercurrent diseases, injuries, or other conditions since second visit. Intake of medicines, other than iron, folate.
- II.C. Iron intake: compliance.
- II.D. Note other medical consultations, hospitalization, sick leave in present pregnancy.

III. Obstetric history

Review relevant issues of obstetric history as recorded at first visit, and as checked at second.

IV. Present pregnancy

IV.A. Symptoms, events since second visit: pain (pre term labour?), bleeding, vaginal discharge (amniotic fluid?). Other specific symptoms or events.

IV.B. Changes in body features or physical capacity, observed by the women herself, husband, or other family members.

IV.C. Fetal movements.

IV.D. Check-up on habits: smoking, alcohol, other.

V. Physical examination

V.A. Blood pressure

V.B. Symphysis-to-fundus distance: record on graph.

V.C. Palpate for multiple fetuses.

V.D. Fetal heart sounds; use hand-held doppler only if no fetal movements are seen, mother feels less fetal movement or she requests it.

V.E. Generalized edema.

V.F. Other alarming signs of disease: shortness of breath; cough, etc.

V.G. If bleeding or spotting; refer.

V.H. Breast examination.

VI. Special test

VI.A. Urine: protein for nulliparous or high risk multiparous.

VI.B. Blood: Hb, all.

VII. Assessment and referral

VII.A Reassess risk based on evidence since second visit and observations at present visit:

- untoward symptoms: referral as required
- evidence of preeclampsia; refer to special unit in the clinic, or hospitalize
- suspicion of fetal growth retardation: (symphysis-to-fundus distance too short): refer and arrange for delivery
- suspicion of twins: refer for confirmation, arrange delivery
- urine test positive for protein: refer
- if Hb continuously < 70 g/l: refer and arrange for delivery
- if Hb > 130 g/l: new appointment at 36 weeks, to check fetal growth, blood pressure and proteinuria.

VIII. Intervention

VIII.A. Iron: continue, all. If Hb on first test < 70 g/l, refer.

VIII.B. If bleeding, refer.

VIII.C. Tetanus toxoid, second injection.

IX. Advice, questions & answers, and appointment

IX.A. Repeat advice given at first and second visits.

IX.B. Advice on measures, action in case of (threatened) labour.

IX.C. Questions & answers: time for free communication.

IX.D. Reconfirm written information on where and whom to call in case of emergency or any other need.

IX.E. Recommendations on lactation, contraception and the importance of the postpartum visit.

IX.F. Appointment: fourth visit: at (or close to) 38 weeks.

X. Record keeping

- X.A. Office record.
- X.B. Home based record.

The Fourth Visit

The fourth will be the final visit and should take place between weeks 36 and 38. Those women (5% - 10%) who will not have delivered by the end of week 41 (complete 41 weeks or 290 days) should be advised to go directly to the hospital for evaluation and possible induction of labour by the best method available. This is recommended considering the unproven benefit of all methods of fetal surveillance commonly used in prolonged pregnancies. Although perinatal mortality is low (Klein, 1989) and routine induction is not always recommended (Rosen, 1992), available evidence from meta-analysis of several randomized trials demonstrates that routine induction of labour after 41 completed weeks is not associated with any major disadvantages, reduces the risk of meconium-stained amniotic fluid and perinatal death (13 trials included in meta-analysis O.R. = 0.23 (95% CI 0.06-0.90), and does not increase cesarean section rates in unfavorable cervix (5 trials included in meta-analysis O.R. = 0.94; 95% CI 0.68-1.32) (Crowley, 1994). Furthermore, it may be possible that it reduces the overall cesarean section rates if induction is correctly performed (11 trials included in meta-analysis: O.R. for CS 0.87; 95% CI 0.76-0.99) (Hannah, 1992; Crowley, 1994).

It is extremely important that women with fetuses in breech presentation should be discovered and referred for obstetric evaluation and external version. External version should be attempted at the hospital, or when disproportion is suspected, elective cesarean section could be considered. Although hospitals' practice will not be influenced, it is expected that if external version is successful, trial of labour will be allowed in these patients. All information on what to do, whom to call, and where to go (which hospital) when labour starts or other symptoms, should be reconfirmed in writing.

The obstetrical care will be completed at this time, returned to the mother, and a copy also sent to the hospital where delivery is planned. During this visit recommendations will be made again on the benefits of lactation and the availability of contraceptive methods at the post partum clinic if desired.

Content of the fourth visit:

I. Personal information

Note any changes or events since third visit.

II. Medical history

II.A. Review of relevant issues of medical history as recorded at first three visits.

II.B. Intercurrent diseases, injuries, or other conditions since third visit. Intake of medicines, other than iron, folate.

II.C. Iron intake: compliance.

II.D. Note other medical consultations, hospitalization, sick leave in present pregnancy, since third visit.

III. Obstetric history

Final review of obstetric history relevant to delivery.

IV. Present pregnancy

IV.A. Symptoms, events since third visit: pain contractions (pre-term labour?), bleeding, vaginal discharge (amniotic fluid?). Other specific symptoms or events.

IV.B. Changes in body features or physical capacity, observed by the women herself or by husband, other family members.

V. Physical examination

- V.A. Blood pressure
- V.B. Symphysis-to-fundus distance: record on graph.
- V.C. Multiple fetuses.
- V.D. Fetal lie, presentation (head, breech, transverse).
- V.E. Fetal heart sound(s) by hand-held doppler only if no movements are seen or referred by patient or she asks for it.
- V.F. Generalized edema.
- V.G. Other alarming signs of disease shortness of breath, cough, etc.
- V.H. If bleeding or spotting: refer.

VI. Special tests

Urine: proteinuria, for nulliparous or high risk multiparae.

VII. Assessment and referral

- VII.A. Reassess risk, based on evidence since third visit and observations at present visit.
 - untoward symptoms: referral as required
 - evidence of preeclampsia: refer, or hospitalize
 - suspicion of fetal growth retardation: (symphysis-to-fundus distance too short): refer
 - suspicion of twins: arrange for hospital delivery
 - suspicion of breech presentation: refer. Hospital delivery mandatory.

VIII. Intervention

- VIII.A. Iron: continue, all.
- VIII.B. If bleeding: refer.

IX. Advice, questions & answers, and appointment

- IX.A. Repeat advice given at previous visits.
- IX.B. Advice on measures, action in case of labour, leakage of amniotic fluid.
- IX.C. Advise on breast feeding.
- IX.D. Questions & answers: time for free communication.
- IX.E. Reconfirm written information on whom to call and where to go (place of delivery) in case of labour or any other need.
- IX.F. Appointment: if not delivered by end of week 41 (state date): go to hospital for check-up.
- IX.G. Appointment for post partum visit. Recommendation on lactation and contraception.

X. Record keeping

- X.A. Office record.
- X.B. Home based record.

Women attending late in pregnancy

It is very likely that a good number of women will not initiate antenatal care early enough in pregnancy to follow the schedule presented above. These women, particularly those starting > 32 weeks of gestation, should have the first visit with cumulative activities of previous visit and after it the ones which correspond to the gestational age. It is expected therefore that the first visit will take more time than a regular first visit. Special care should be taken that all previous activities are conducted at this time.

The Post-Partum Visit

Although the post-partum visit is universally recommended for perinatal care, it is seldom done in most developing countries. The importance of this "post" and "pre-conception care" visit has been recently emphasized by the expert panel on prenatal care (Rosen et al., 1991). The determinants of some pregnancy outcomes, such as low birth weight and the

Table 3 : CONTENT OF THE BASIC COMPONENT OF THE
NEW ANTENATAL CARE PROGRAMME

ACTIVITY	PRENATAL VISITS (approximate week gestation)			
	1st *	2nd (26 wk)	3rd (32 wk)	4th (38 wk)
Pregnancy test (only if req. at 1st trimester & no clinical evidence of preg.)	☒	--	--	--
Medical/Ob history (risk evaluation)	■	--	--	--
Question of Rh immunization with fetal/newborn disease in previous pregnancy	☒ multiparous	--	--	--
Complete clinical examination	■	--	--	--
Clinical examination for severe anemia	■	■	■	■
Ob exam (+) Gyn exam/detection of symptomatic STDs	■ routine vaginal exam **	■ ob exam	■ ob exam	■ ob exam
Maternal weight/height	■	--	--	--
Maternal weight (follow-up)	--	☒	☒	☒
Uterine height	■	■	■	■
Gestational age assessment	■	■	■	■
Blood pressure	■	■	■	■
- Blood type / Rh	■	--	--	--
- Hb	☒	☒	■	--
- Syphilis	■	--	--	--
- Urine test	■ ***	☒	☒	☒
Tetanus toxoid	■	--	■	--
Folic acid/Iron supp.	■	■	■	■
Fetal heart rate	☒	☒	☒	☒

■ for all women
 * for all women at first contact with clinic, regardless of gestational age
 ** could be postponed to second or third visit
 ☒ only in some cases:
 a) proteinuria: nulliparous or with previous preeclampsia or hypertension;
 b) fetal heart rate: only if requested or no fetal movements seen or reported;
 c) maternal weight: only those with low weight/height at 1 visit or obese women
 d) anemia: ☒ only if signs of severe anemia
 *** multiple dipstick
 (+) ob exam: # fetuses, fetal situation & presentation

Table 3 : CONTENT OF THE BASIC COMPONENT OF THE
NEW ANTENATAL CARE PROGRAMME
(cont'd)

ACTIVITY	PRENATAL VISITS (approximate week gestation)			
	1st *	2nd (26wk)	3rd (32 wk)	4th (38 wk)
Recommendations for: urgent consultation next visit/schedule treatment/medical conditions	■	■	■	■ date of wk 41 and instructions
Referral to hospital if needed	⊗	⊗	⊗	⊗
Detection of breech presentation & referral for external version	—	—	—	■
Instruction for referral for adequate level of delivery	—	—	⊗	⊗
Recommendations for lactation			■	■
Contraception	—	—	■	■
Pre-conceptual care	—	—	—	⊗
Activities to reduce smoking	■	■	■	■
<p>■ for all women * for all women at first contact with clinic, regardless of gestational age ⊗ only in some cases: <u>delivery</u>: if previous obstructed labor, hemorrhage or C.S.; <u>pre-conceptual care</u>: infant with NTD or other congenital malformation</p>				

Table 4 : BASIC ANTENATAL CARE PLAN BY VISIT

The First Visit

- Medical/Ob history (risk evaluation)
- Clinical examination / severe anemia
- Ob exam / Gyn exam (can be postponed until second visit)
- Maternal weight / height
- Blood pressure
- Gestational age estimation
- Uterine height
- Syphilis, detection of symptomatic STDs
- Urine test (multiple dipstick)
- Tetanus toxoid
- Fe / Folic acid supplementation
- Recommendation for urgencies / hot line for emergencies
- Complete antenatal card
- Blood type and Rh

The Second Visit and subsequent visits

- Blood pressure to nulliparous & women with previous preeclampsia/age groups
- Obstetric exam
- Gestational age estimation
- Fetal heart rate
- Uterine height
- Urine test (only nulliparous/women with previous preeclampsia)
- Fe / Folic acid supplementation
- Clinical examination for anemia
- Maternal weight (only women with low weight/height 1st visit)
- Recommendation for urgencies
- Complete antenatal card

For the Third Visit - add:

- Repeat syphilis & g.c. test for high-risk women
- Hb
- Tetanus toxoid (second dose)
- Instructions for adequate place of delivery
- Recommendations for lactation / contraception

For the Fourth Visit - add:

- Detection of breech presentation & referral for external version

Furthermore, a recent attempt was made to evaluate the items which could mediate the relationship between routine prenatal care and birth weight. There were eight activities considered necessary to be included in prenatal care to achieve an impact on LBW: risk assessment, urine culture, smoking cessation, alcohol and drugs avoidance, low weight and referral, follow-up of no shows and weight gain monitoring (Petitti et al., 1991). The new model includes most of them except weight gain, which is recommended to a subgroup of women; although it does not recommend routine urine culture, it has one rapid screening mechanism for bacteriuria.

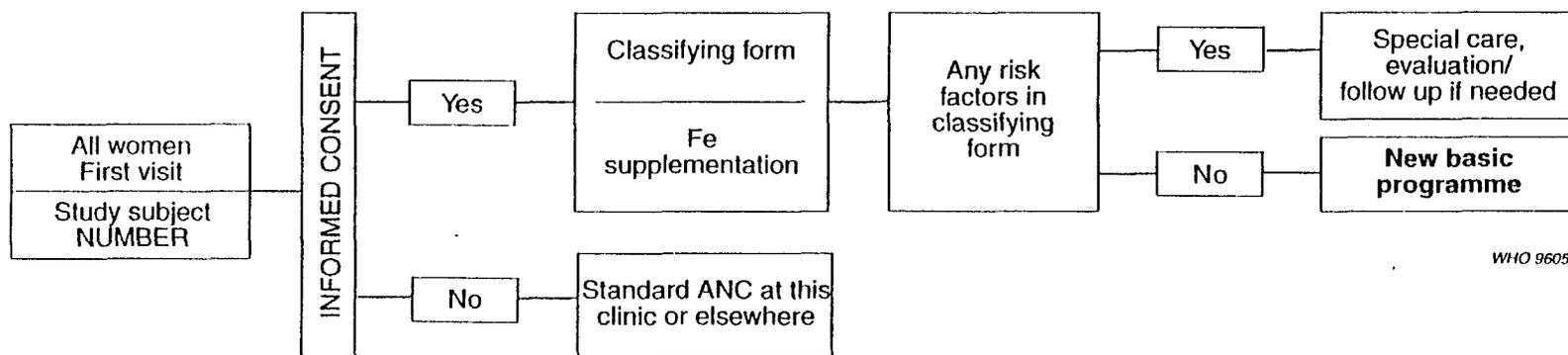
Flow Chart: Figure 2 presents the Flow Chart of patients enrolled in the new programme and the two levels of care available. At the first antenatal visit in the clinics randomized to the system, patients will be asked to provide informed consent to participate in the study. Those who agree to do so will be classified as to whether or not they require special care (classifying form). It is very likely that clinics already have a risk score system, which will have to be replaced by Classifying form only in those clinic randomized to the new programme.

Women eligible for the basic component of the new programme can be referred, if needed, to a nutrition clinic, psychiatric unit or to a tertiary hospital for delivery. Women with only risk factors for delivery complications but with normal pregnancies will follow the basic component of the new programme. It is considered that no additional prenatal visits are needed for women requiring social or nutritional support; this also is the same for women with only a history of intrapartum complications.

Women who are not eligible for the basic component of the new programme (from "classifying") will receive care either at a referral hospital or evaluated at the same clinic by a consultant. The decision of the place and content of care for these patients will be based on current medical practices in the study sites. Table 5 presents an example of patient flow analysis for a clinic recruiting 550 patients in a 12-month period. In such a case, it is expected that each clinic will have an approximate total of 200 pregnant patients (new and continuing) in the month of highest recruitment, plus extra visits for high risk patients as

Figure 2 :

WHO Antenatal care randomized trial; flow chart of patients enrolled in clinics *randomized to the intervention group*



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Table 5 : PATIENT FLOW ANALYSIS : ANTENATAL CARE TRIAL

Month	VISIT				Total Clinic visits
	First	Second S + US	Third S + US	Fourth S + US	
1	46				46
2	46				46
3	46				46
4	46	44 + 5			95
5	46	44 + 5	42 + 6		143
6	46	44 + 5	42 + 6	40 + 8	191
7	46	44 + 5	42 + 6	40 + 8	191
8	46	44 + 5	42 + 6	40 + 8	191
9	46	44 + 5	42 + 6	40 + 8	191
10	46	44 + 5	42 + 6	40 + 8	191
11	46	44 + 5	42 + 6	40 + 8	191
12	46	44 + 5	42 + 6	40 + 8	191
13		44 + 5	42 + 6	40 + 8	145
14		44 + 5	42 + 6	40 + 8	145
15		44 + 5	42 + 6	40 + 8	145
16			42 + 6	40 + 8	96
17				40 + 8	48
18					
Total	552	588	576	576	2292

Assumes: 12 months to recruit 550 women (46 per month)
 First visit at 12 weeks
 Second visit at 26 weeks, plus 10% unscheduled visits.
 Third visit at 32 weeks, plus 15% unscheduled visits.
 Fourth visit at 38 weeks, plus 20% unscheduled visits.

medically required and who are not referred to the hospital. It is recommended that each study site construct similar flow analysis adapted to their average clinic size.

4.5 The Control Group

Traditional antenatal care presupposes monthly visits from the start (as early as possible) to week 28, then visits at two-weekly intervals until week 36, followed by weekly intervals until birth or the end of week 42, at which time post-term referral is common for those who have not yet developed spontaneous labour contractions.

Although this timing is not implemented exactly in all study settings, it is close to most of the recommendations and the actual care provided in private practices in the developing world. There would not be major disagreements among obstetricians in identifying this as the "ideal" programme. The contents of each visit may vary according to the location, for example, regarding screening test. In principle, however, the same routine elements are included in each visit. In practical terms, few public clinics in urban areas of developing countries complete this protocol, even for those women who attend early in pregnancy.

During the preparatory stage of the study, a survey was conducted in all clinics for a baseline description of antenatal care procedures and available resources, adapted from a study recently conducted in Europe (Maratos, 1986). This survey included a random sample of antenatal care visits taken at baseline and once more during the study. A simplified form was filled out, including information on crucial elements of content, interventions and use or resources in both the control and intervention clinics. Clinics, randomized to continue with the traditional care, serve as the comparison group. The personnel were informed of the study and its objectives, before randomization and it is expected that the clinics will themselves update their procedures and attempt to follow the recommended (Western type) protocols more closely (Hawthorne effect). As the main factors related to the present organization of prenatal care have not been changed, this improvement may not be totally achieved; however, it is very likely that the control clinics will offer, particularly to those women attending in early pregnancy, a prenatal care programme more efficient than the one in place before the study was initiated.

As long as this improved care is kept within the framework of traditional care, it should not invalidate comparisons. In fact, it will give the study a stronger arguments in support of the new programme by eliminating the reaction that the new programme is similar to or better than the "old" only because the old was very inefficient. Attempts will be made to demonstrate that the new programme is equal to or better than a "good traditional prenatal care" system.

4.6 Treatment allocation

As already discussed, practical considerations (contamination, simplification of organization of trial, large sample size) demand that the principle of randomization by unit is followed rather than by individual pregnant woman. The benefits and feasibility of this design have been demonstrated recently in two trials evaluating perinatal procedures (Grant, 1989; Bullough, 1989).

Therefore, this is a multi-centre, randomized controlled trial with "cluster allocation". The clusters (between 300 to 500 women in each), consist of a series of selected antenatal care clinics. The clusters were stratified by study site (country), clinic size (number of patients) and randomized within each stratum.

Within each stratum, the clinics were allocated to the new programme or to the "control" group according to a pre-set random code which were independently prepared and not revealed to the clinics' staff until all preparations for participation were completed in each site and training was initiated in the intervention clinics. Recruitment and trial registration will be preceded by a pilot phase, during which the rules and procedures of the new package in particular were tested.

4.7 Outcome Variables (end-points)

4.7.1 General principles

Outcome variables can be classified as primary or secondary, process or impact indicators of cost of the intervention and satisfaction and perceived quality of care. A trial should select as its primary outcome variables those that are:

- (a) more affected by the intervention;
- (b) represent an important clinical or health problem;
- (c) can be recorded as objectively as possible or by an independent observer;
- (d) that occur frequently enough to provide sufficient statistical power. The study will have power for this incidence of the event.

Antenatal care is a complex set of activities aimed at reducing maternal mortality by reducing the likelihood that a pregnant woman will experience a serious complication of pregnancy or childbirth, and by improving the maternal and fetal outcomes of women with complications (McCarthy and Maine, 1992). It is clear that maternal mortality is a rare event and that the sample size required would be unrealistic; thus, a series of surrogate measures and a maternal morbidity index should be used.

Antenatal care should also identify a fetus at risk and prevent its death by treating or delivering it. The care can reduce the incidence of severe intrauterine growth retardation and preterm delivery, and by this mechanism further influence intrapartum and neonatal death. However, intrapartum deaths are mostly affected by factors related to labour and delivery and are less likely than fatal or neonatal death to be affected by antenatal care. Antenatal care has little influence in the death of infants with normal birth weight, except, for example, diagnosing breech presentation and acting upon it.

Furthermore, the effect of prenatal care on perinatal mortality in populations with high perinatal mortality is confounded by the proportionally smaller contribution of fetal death. Intrapartum death in such populations represents a much higher proportion of perinatal death due to lack of delivery services and birth trauma. In these populations, low birth weight is also very prevalent, and these infants are likely to be more vulnerable to intrapartum and neonatal events (Kline et al., 1989).

In summary, what is the optimal primary outcome measure for the ANC study?

1. Antenatal care is a complex set of activities designed to maintain health; reduce the occurrence of disease and complications during pregnancy, childbirth and the post-partum period; and to reduce maternal mortality and fetal death. It is clear that if only maternal and fetal death are considered, these are rare events and the sample size required to evaluate the effect of the intervention would be large.
2. Perinatal mortality can be seen as a global indicator of fetal/newborn health.
3. However, perinatal death is related to several etiological factors:
 - (a) congenital malformations;
 - (b) IUGR/pre-term birth;
 - (c) intrapartum complications;
 - (d) neonatal care;
 - (e) maternal diseases;
 - (f) combinations of the above.

4. Antenatal care has little effect on the rate of perinatal death among normal birth weight infants. In the Oxford region from 1984-1987, only 6% of all intrapartum of postpartum deaths were singleton babies > 37 weeks without congenital malformations or evidence of severe infection. In both developed and developing countries, pre-term delivery accounts for 60 to 80% of all perinatal deaths (Rush, 1976).
5. Perinatal death is influenced by the quality of intrapartum and neonatal care which is mainly unrelated to ANC. In a recent review of all perinatal deaths in the Oxford region, only 47% of babies who died were considered to have a complicated antenatal history (Gaffney et al., 1994). Neonatal intensive care units do remarkably well in "rescuing from death" very preterm infants (Johnson A. 1995).
6. Excluding congenital malformation and intra-partum death, it is very unlikely that ANC will influence perinatal mortality without changing the rate of pre-term delivery and IUGR.
7. Although perinatal death is a dramatic event, prematurity, specially very preterm births apart from being the major instigator of neonatal death, is related to neurological handicaps, motor, sensory and cognitive disorders which are recognized to entail family suffering, cost and social implications. The long-term implications of pre-term delivery are very well-documented in the literature.
8. Trials that are expected to have modest improvements or no improvements over a more complex system (as in the ANC) on relatively rare outcomes, can use surrogate measures to these primary outcomes or combined index (e.g. maternal morbidity index, fetal/newborn health index). (Villar et al., 1990).

In the following sections, we will discuss specific maternal and fetal outcomes.

4.7.2 Maternal variables

The degree to which antenatal care may improve different outcomes is not as easily assessed as one might first surmise. Some of the adverse outcomes which dominate the lists of causes of maternal mortality result from dramatic episodes which arise shortly before or during the actual birth. Whether elements of antenatal care can prevent or ameliorate such outcome, is, still a topic under discussion. Some examples which follow may clarify the issue.

Complications arising from preeclampsia and eclampsia, obstructed labour, intra- and post-partum bleeding, as sepsis due to local infection are major causes of maternal death (Royston & Armstrong, 1989). Although eclamptic fits may occur without any clinical antecedent preeclampsia or other warning, cases may be avoided if preeclampsia is diagnosed and the conditions monitored carefully until timely delivery. This may further explain the different eclampsia rates among populations and time periods (Douglas K, 1992), while the preeclampsia incidence is relatively stable across populations. Obstructed labour may in some cases be anticipated through the case history, by maternal height and physical examination in late pregnancy, and appropriate actions for operative delivery taken. Bleeding complications may be reduced through antenatal treatment of preeclampsia (abruptio placentae) and emergencies anticipated by early diagnosis of placenta previa. Pre-existing anemia may worsen the consequences of bleeding.

The primary outcome of the trial in relation to maternal conditions will be the rate of "maternal morbidity indicator index". This is defined as the presence of at least one of the following severe conditions: proteinuric-preeclampsia, eclampsia or severe hypertension

(> 160/110 mm Hg) during pregnancy or within 24 hours of delivery; postpartum anemia < 90 g/l of hemoglobin and severe urinary tract infection/pyelonephritis, defined as requiring antibiotic treatment or hospitalization. The rate of this index has been estimated to be above 10% in all study sites.

4.7.3 Perinatal Outcomes

For the purpose of assessing possible effects of antenatal care on perinatal outcome, it is important to distinguish between intrauterine events (with fetal death as the extreme example) and events occurring after the birth of a living child.

Adverse intrauterine conditions may lead to permanent disability or impairment of mental or physical functions. Chronic malnutrition may lead to growth retardation and fetal death. Some fetal conditions can be detected and risk assessed through antenatal surveillance (smoking, syphilis, fetal growth retardation). Some risk factors can be partially removed through changes in behavior (smoking), treatment (syphilis) or by induction of birth to save a severely growth-retarded fetus (elective versus emergency cesarean section).

Death or disease during the first week of life is likely to result from intrauterine conditions which may occur either before or during birth, but also from events after birth, particularly among preterm and LBW infants. When perinatal mortality diminishes, as it has in industrialized countries, the relative share of stillbirth is higher (about 50% of perinatal mortality). The primary outcome of the study in relation to fetal conditions will be the **rate of low birth weight (< 2500 g)**. It is considered very unlikely that ANC will influence perinatal mortality without changing the rate of LBW. Because of the difficulties in obtaining reliable gestational age for this large population under different clinical care, it is not possible to differentiate between preterm delivery and SGA as is recommended in the literature.

4.7.4 Process variables

The definition of process variables will not include a description of the antenatal care system, such as number of antenatal care visits and content of each visit, because this is the description of the implementation of the treatment or intervention, and not a process variable. The intervention will be described and its compliance documented as is done in clinical trials (urine or serum level of a drug or number of tablets taken).

Table 6 enumerates the outcome variables of the study:

4.8 Sample Size

4.8.1 Background

Sample size estimates depend on a number of practical and statistical considerations, some of which can only be surmised and several of which are somewhat arbitrary. Factors that influence sample size are:

1. major outcome variables of interest;
2. pre-intervention level of the major end-points, and the variability of the endpoints in the absence of intervention;
3. effect of intervention on the endpoints selected for study;
4. the chance of claiming that an effect intervention has occurred, when in fact, no effect was present: the alpha level corresponding to the statistical test of significance;
5. the chance of failing to detect an effect of intervention, when in fact, an effect was present: $\beta = 1 - \text{power of the test of significance}$;
6. participation rates of both individuals and entire clusters;

Table 6 : Outcomes of the ANC Randomized Controlled Trial

A. PRIMARY OUTCOMES	Question number in Data Collection Form(s)	Rate
Rate of maternal morbidity indicator index ⁽⁺⁾	See individual items	> 10%
Rate of LBW (<2500g)	50	> 10%
B. SECONDARY OUTCOMES		
Incidence of proteinuric ^(*) -pre-eclampsia or eclampsia	27	
Prevalence of post partum anemia (hemoglobin <90g/l) ^(**)	38	
Incidence of severe urinary tract infection/pyelonephritis (requiring antibiotic treatment ^(***) or hospitalization)	28 and hospital admission	
Rate of treated syphilis and any other STDs	31	
Rate of post-partum positive syphilis test ^(***) (among women without treatment during pregnancy)	39	
Rate of incomplete tetanus immunization	21	
Rate of post partum hospital stay ≥ 7 days for maternal complications	41-42	
Rate of IUGR ^(#)		
Rate of preterm delivery (<37 weeks)	52	
Rate of spontaneous & PROM pre-term delivery : <35weeks : 35-36 weeks	36	
Rate of medically indicated pre-term delivery : <35 weeks : 35-36 weeks	36-37	
Rate of breech presentation at birth	48	
Rate of very LBW (<1500 g)	50	
Rate of Apgar score <5 at 5'	53	
Rate of I.C.U. stay > 2 days	55 (c)	
Rate of fetal death	49	
Rate of pre-discharge neonatal death	56	

* Proteinuria of 2.0 g or more in 24h or 2+ or more on qualitative examination (dipstick)

** Requires postpartum blood samples

*** Excluding the antibiotics given to treat asymptomatic bacteriuria

+ Maternal morbidity indicator index: the presence of at least one of the following:

proteinuric-preeclampsia or eclampsia (during pregnancy or within 24 h of delivery; post-partum anemia (<90 g/l); severe urinary tract infection/pyelonephritis (requiring antibiotic treatment or hospitalization)

If LNMP not available, use the best "obstetric" estimation; below 10th percentile of international standard

OUTCOMES OF THE ANC RANDOMIZED CONTROLLED TRIAL
(contd.)

C. PROCESS OUTCOMES	Question number in Data Collection Form(s)	Rates
Rate of antenatal hospital admission - total by cause	Hospital admission form	
Rate of elective and emergency cesarean section associated with pregnancy complications (****)	36-46-47 of Summary form	
Days of hospital admission during pregnancy (median)	Hospital admission form	
D. COST OF ANC	Mean (SD) in US\$	
To the health service		
To the patient		
E. SATISFACTION AND PERCEIVED QUALITY OF CARE (only in random sample)		
By the health workers		
By the patient		

**** Excluding intrapartum cesarean section for fetal distress or cephalopelvic disproportion

7. duration of study;
8. loss to follow-up;
9. randomization by cluster;
10. use of randomized pairs or randomized blocks to increase the precision of comparisons;
11. study areas (countries; sites within country; clinics or hospitals within areas).

Changing the specification of any one of the above factors can have a major effect on the estimate of the sample size. Some of these factors have specific relevance in reference to the present protocol.

The major endpoint

Any one of the many endpoints of interest itemized in the protocol can be used to estimate the required size of this study, with the sample size varying by the endpoint chosen. Among these endpoints, there are two primary outcomes of major public health importance which the new programme must demonstrate will not increase: namely, the maternal morbidity index and low birth weight. Thus, the average minimum rate obtained for individual rates from areas to be enrolled in the study (about 10%) will be used to plan the size of the proposed investigation.

Baseline values

It is reasonable to expect to identify areas where this rate (10%) ranges from a low of about 7 per 1000 live births to a high of about 13 per 1000 live births. Since the areas of study will not be homogeneous in their LBW, the estimate of sample size has to take this into account. The sample size analysis also has to account for the use of cluster randomization, rather than individual patient randomization (see 4.2.2., Unit of Randomization).

Effect of Intervention

The new system of antenatal care is expected to have no major adverse effect on perinatal mortality. The design of study to reliably confirm such an hypothesis, if indeed it is true, would be prohibitive in terms of the required number of patients and study areas, unless, of course, the new system of care has a substantial beneficial effect, which is not expected either. Thus, before attempting to confirm an hypothesis of "minimal" or "negligible" effect, it seems sensible first to plan a study designed to determine whether such a supposition is even plausible.

Randomization

The unit of randomization will be a **cluster**, which will consist of a clinic or a group of small clinics within a geographic or administrative area (see 4.2.2, Randomization by Unit).

A gain in design efficiency is possible in principle by using randomized pairs with a corresponding pair-matched analysis. The gain in efficiency from pairing depends on how close the matching can be done relative to the variability in rates across the study areas. Although this design is attractive, there are several associated drawbacks that make it a less acceptable option (Martin et al., 1993). The most important limitation is the inability to consistently estimate the within-cluster intraclass correlation coefficient with respect to the response variable of interest. A detailed description of the limitation and the implication for data analysis can be found in Donner and Klor (1994).

Study areas

The particular areas of study, the countries, clinics and hospitals should have an infrastructure that can support an intervention trial, including sufficient numbers of

patients for follow-up. The areas chosen for study span a range of primary outcome rates, so that results of the investigation can apply across a spectrum of settings.

4.8.2 Sample size

(The determination of sample size included here has been prepared with the support of Gilda Piaggio PhD.)

The determination of sample size presented here uses a stratified cluster randomization design to compare the intervention with the standard treatment.

The outcome dichotomous variable is low birthweight: there are four or five strata or countries, the clusters being the clinics or hospitals within the country. By fixing the time period for recruiting, the investigator can control the cluster size.

The question addressed is the determination of the total number of individuals needed and the number of clusters in each stratum, to achieve a certain power and confiability in comparing the two rates. Formula 2 of Donner (1992) will be used to obtain an answer.

The calculations are made in two steps, the first step being the estimation of the intra-cluster correlation, and the second step is the implementation of Donner's Formula 2 (Donner, 1992).

Estimation of the intra-cluster correlation

Estimation of the intra-class correlation was done using standard formulas applied to dichotomous data as described in Fleiss (1981), Formula 13.42, using a data set from four clinics and four hospitals in Argentina with the dichotomized variable low birth weight. The

estimation was made for the future study assuming cluster sizes of 300, 450 and 600 (md), using the components of variance estimates from the data set to compute the Between and Within Mean Squares (BMS and WMS respectively) needed in Formula 13.42. The estimates, done separately for hospitals and clinics, were respectively .00005 and .00008, which average .00065.

Implementation of Donner (1992)'s Formula 2

The stratum-specific success rates P_c were taken to be equally spaced from .07 to .13 (four strata, $i=1, \dots, 4$), or from .06 to .14 (five strata, $i=1, \dots, 5$). Calculations were made also for five strata because there is the possibility to include a fifth country in the study.

Two values were assumed for the odds ratio (OR), namely 1.16 and 1.20, and the stratum-specific success rates P , $i=1, \dots, 4$ or 5 were derived from the P_c 's and the OR's. Three values were taken for the cluster sizes, namely 300, 450 and 600. A constant number of clusters in each stratum was assumed, so that

$$t_i = \frac{m_i}{4} = 1 \quad \text{or} \quad t_i = \frac{m_i}{5} = 1$$

$$\sum_{i=1} m_i \qquad \sum_{i=1} m_i$$

Using the above values and the value for the intra-class correlation coefficient estimated from the Argentinian data set, as well as other values close to it, Formula 2 of Donner's was implemented for a two-sided test, a level of significance of .05 ($z_\alpha = 1.96$) and a power of 80% ($z_\beta = .842$).

The results are shown in Tables 7a, 7b and 7c. Please note that Table 7c presents sample size calculations for $\beta = 0.10$ or a power of 90%. This is done to evaluate the effect on the sample size of an approach to reduce the risk of false negative results. For example, take the usual objective of showing that the new model of ANC is more effective than the traditional model:

		REALITY	
		Equivalent	Not equivalent
DECISION	Equivalent		β
	Not equivalent	α	

β = Probability of concluding that the two methods are equivalent, when in fact they are not (say = 0.10).

Suppose the true O.R. = 1.18; we observe, say OR = 1.10. If SE (LnOR) is 0.05,

$$x^2 = \frac{\text{LnOR}^2}{\text{SE}^2 (\text{LnOR})} = 3.6 < 3.84$$

If we conclude that “methods are equivalent”, we are making a mistake. We will do so whenever we observe $\text{OR} < 1.11$. We want then that the probability of making this mistake to be $\beta < 0.10$. The implications of this requirement on the sample size are presented in Table 7c.

From these tables we can see that for $\alpha = 0.05$ and $\beta = 0.20$ for an OR 1.18 and four study sites, a total sample size of approximately 16,000 women is needed, distributed in ten clinics of 450 pregnancies per study site (Table 7a). If we have five study sites, eight clinics per site will be needed (Table 7b). However, we would like to have a power of 90% ($\beta = 0.10$); we will need twelve clinics of 450 pregnancies in each of the four study sites for a

Table 7(a): Total number of individuals (N) and number of clusters per stratum per group (n), for P_c ranging from .07 to .13 in four strata $\alpha = 0.05; \beta = 0.20$

ρ	OR	Size of temporal block m_1					
		300		450		600	
		N	n	N	n	N	n
0	1.16*	15040	7	15040	5	15040	4
	1.18**	12016	5	12016	4	12016	3
	1.20	9841	5	9841	3	9841	2
.00065	1.16	17963	8	19430	6	20896	5
	1.18	14352	6	15523	5	16695	4
	1.20	11753	5	12713	4	13672	3
.001	1.16	19537	9	21793	6	24049	5
	1.18	15609	7	17411	5	19214	4
	1.20	12783	6	14259	4	15735	4
.002	1.16	24034	10	28546	8	33058	7
	1.18	19202	8	22807	7	26411	6
	1.20	15725	7	18677	6	21630	5

N is value obtained from formula (2) of Donner (1992).

Note: $300 \times 4 \times 2 \times n \approx N$. This is only approximate because values of n have been rounded up to give integer numbers.

ρ = intracluster correlation coefficient; shaded ρ was obtained using data from hospitals & clinics from one of the study sites (Villar et al, 1994)

O.R. - odds ratio

* O.R. = 1.16 corresponds to $P_c = 0.10$ and $P_i = 0.114$

** O.R. = 1.18 corresponds to $P_c = 0.10$ and $P_i = 0.116$

Table 7(b): Total number of individuals (N) and number of clusters per stratum per group (n), for P_c ranging from .06 to .14 in five strata $\alpha = 0.05$; $\beta = 0.20$

ρ	OR	Size of temporal block m_1					
		300		450		600	
		N	n	N	n	N	n
0	1.16*	15097	5	15097	4	15097	3
	1.18**	12062	4	12062	3	12062	2
	1.20	9879	4	9879	3	9879	2
.00065	1.16	18031	6	19503	5	20975	4
	1.18	14406	5	15582	4	16758	3
	1.20	11799	4	12762	3	13725	3
.001	1.16	19611	7	21875	5	24140	4
	1.18	15669	6	17478	4	19287	4
	1.20	12832	5	14314	4	15796	3
.002	1.16	24125	8	28654	7	33183	6
	1.18	19275	7	22894	5	26512	5
	1.20	15786	6	18750	5	21713	4

N is value obtained from formula (2) of Donner (1992).

Note: $300 \times 5 \times 2 \times n \cong N$. This is only approximate because values of n have been rounded up to give integer numbers.

ρ = intracluster correlation coefficient; shaded ρ was obtained using data from hospitals and clinics from one of the study sites (Villar et al, 1994).

O.R. - odds ratio

* O.R. = 1.16 corresponds to $P_c = 0.10$ and $P_1 = 0.114$

** O.R. = 1.18 corresponds to $P_c = 0.10$ and $P_1 = 0.116$

Table 7(c): Total number of individuals (N) and number of clusters per stratum per group (n), for P_{ic} ranging from .07 to .13 in four strata $\alpha = 0.05$ (2-sided) and $\beta = .10$

ρ	OR	Size of temporal block m_1					
		300		450		600	
		N	n	N	n	N	n
0	1.16*	20134	9	20134	6	20134	5
	1.18**	16085	7	16085	5	16085	4
	1.20	13173	6	13173	4	13173	3
.00065	1.16	24046	10	26009	8	27972	6
	1.18	19211	8	20780	6	22348	5
	1.20	15733	7	17017	5	18302	4
.001	1.16	26153	11	29173	9	32193	7
	1.18	20895	9	23307	7	25720	6
	1.20	17111	8	19087	6	21063	5
.002	1.16	32173	14	38213	11	44253	10
	1.18	25704	11	30530	9	35355	8
	1.20	21050	9	25002	7	28953	6

N is value obtained from formula (2) of Donner (1992).

Note: $300 \times 5 \times 2 \times n \approx N$. This is only approximate because values of n have been rounded up to give integer numbers.

ρ = intracluster correlation coefficient; shaded ρ was obtained using data from hospitals and clinics from one of the study sites (Villar et al, 1994).

O.R. - odds ratio

* O.R. = 1.16 corresponds to $P_c = 0.10$ and $P_t = 0.114$

** O.R. = 1.18 corresponds to $P_c = 0.10$ and $P_t = 0.116$

total 21,000 patients (Table 7c). Thus, the study will aim at recruiting at least four study sites which can provide twelve antenatal care clinics of 450 pregnancies during no more than 18 months of patient enrollment.

4.9 Data Management

A general model for data management is presented here; however, there are some practical considerations at different study sites which have been incorporated locally.

4.9.1 Data Collection

The data collection system of the trial is designed to avoid any additional work for the staff of the clinics. In each participating clinic, one of the staff will be responsible for monitoring medical records and in the intervention clinics, the classifying form.

Mothers will be identified in a record book located at each clinic by subject number, name, address, date of birth, expected date of delivery, subject number and clinic record number starting the first day of the study. To ensure confidentiality, this trial book should be accessible only to responsible officers of the trial. On the trial forms to be completed at the hospital level, names will be omitted and replaced by a subject number, clinic and hospital medical record number, which will be the key identification for each subject in case that additional information is needed at the clinic or hospital level.

Summary data collection ("summary" and "hospital admission" form) will be completed by the "hospital data clerk", who will be responsible for data collection and management at that hospital. This person will complete these forms within 24 hours of delivery.

Basic information will be collected on the content and timing of antenatal care activities in the two arms of the trial (intervention and control). A detailed data collection form describing antenatal care procedures will be added for a random sample of women (10% of total sample) in both groups for a better description of the traditional and new antenatal care programmes, and obtained at the clinic from the medical records. This will be implemented again one year after the initiation of the trial.

Forms will be reviewed again at the hospital with support from the corresponding clinic (if needed) for range errors, logical responses, missing data and overall completeness. Only complete forms will be sent to the data entry and quality control unit located at each study site.

At this unit, following standardized procedures coordinated from Geneva by the Statistics and Data Processing Unit of HRP/WHO, data will be entered and a common error programme will be used for review and cleaning of information. It is expected that only clean data in standard computer format will be sent to the study coordinating centre.

Data collection forms are included in Appendix I.

4.9.2 Protocol Compliance

The field director in each site will make visits at least monthly to each antenatal care clinic, including the control clinics. During this visit, they will review medical records for completeness and obvious errors. Furthermore, in collaboration with the physician coordinator, a random number of cases in the intervention clinics will be reviewed to evaluate how the prenatal care was completed documenting deviations from the study protocol and periodically discussed with the clinicians involved; protocol compliance will be reinforced.

These mechanisms will ensure the early detection of problems in implementation of the protocol.

During the field director's visits to the control clinics, there will not be a formal meeting with personnel; rather, attempts will be made to detect any major departure (e.g. equipment, new protocols, new extra staff) from the regular antenatal care system as it was described at the initiation of the study.

There will be a monthly meeting of data clerks, study coordinators and data entry personnel to review the information collected and discuss the implementation of the protocol.

A Formal Survey describing the ANC procedures will be implemented in all clinics (Intervention and Control) to evaluate the compliance with the antenatal care procedures of both arms of the trial. At baseline (before randomization) and one more time within the last 3 months of patient recruitment one clinic day will be randomly selected by the coordinating unit of the trial. During that day all patients attending antenatal care after the first visit will be reviewed for a detailed description of ANC procedures. Data will be obtained from medical records and from any clinical documentation available. Clinic staff will not be involved in this survey and the communication to them of this activity should be as little as possible. A general description of the clinic staff such as year of graduation, gender of MDs, will also be collected. The Study Field Director will be responsible for collecting these data. The details are included in Appendix II.

4.9.3 Data Quality Control

In a trial of this magnitude, one of the first priorities is to maintain uniformity in data collection, as well as careful documentation of data quality. An internal system for monitoring

the quality of the data will be instituted; this will include a series of small studies aimed at monitoring data reliability and agreement among observers in each site. In the Guatemalan perinatal study (Villar et al., 1988), this mechanism has been shown to benefit the quality of data collected. A system of supervision and monitoring the data collection procedures will be implemented after the standardization period (Villar et al., 1989).

A source of bias in data collection is likely to occur in this study. It is based on the desire of personnel and hospital data clerks to report better results even in the control groups (Sacristan et al., 1992). Special efforts will be made to mask hospital personnel of the antenatal care status and to document the following at all hospitals: stillbirth, early neonatal death, emergencies, transfer to/from other hospitals or departments of medicine or intensive care (for maternal reasons). Comparisons will be made of pregnancy outcomes between the study sample and the total population served at the hospital.

4.10 Analysis plan

Data entry and preliminary checks for error and internal validity will be done at each study site. Analyses will be conducted at a central level after the overall plan is accepted by the Principal Investigators and the Steering Committee.

4.10.1 Final analysis

All principal analyses will be based on the clusters as allocated in the randomization to the two programmes of antenatal care ("intention to treat"). Information will be presented for the following areas:

- sample description by intervention/control and site;

- characteristics of women at first antenatal visit in the intervention and control groups: overall and by stratum;
- analysis of the content of the intervention and the antenatal care received in the control group:
- evaluation of process variables;
- evaluation of primary outcomes;
- evaluation of secondary outcomes;
- stratified analysis of primary outcomes by the following a priori selected predicting variables:
 1. Size of the clinics: small, medium, large (following definitions of stratum);
 2. Low risk-high risk;
 3. Gestational age at first visit (early vs late attendance);
 4. Singleton-multiple pregnancies.

The study design will generate approximately 50 clinics with a number between 450 and 500 patients each. The primary question of the trial is whether or not patients seen in the experimental clinics differ from those in control clinics with respect to the primary outcomes of the study (see Section 4.7: Outcome Variables).

Since sample size calculation were conducted using the usual Mantel-Haenszel statistics modified to adjust for the cluster design, data analysis also can be performed using women as the analytical unit (individual rather than cluster analytical unit). The use of the mother as analytic unit allows for exploring secondary analysis such as the relationship between maternal baseline characteristics and other outcomes using a generalized equation approach (Liang and Zeger 1986). The main analytic technique will be an application of the Manatel-Haenszel test adapted to the cluster design (Donner 1992).

Appendix III presents a set of dummy tables to be completed during the analysis using cluster as the analytic unit. Accordingly, data will be collected primarily to complete these tables.

4.10.2 Interim analysis

A Data and Safety Monitoring Committee will be appointed; members will have no direct involvement in the trial. The role of the Committee review of logistics, protocol compliance, efficacy and safety issues and other ethical issues (Armitage, 1991).

The Committee will give advice on matters related to the conduct or stopping of the trial on issues related to safety. It will have three full members: an obstetrician, an epidemiologist and a statistician, who will be joined by the senior statistician of the research team and the Chairman of the Steering Committee. There is likely to be one meeting early in the trial to evaluate quality of the data, as well as review arrangements for data processing.

4.11 Dissemination of results and implementation of findings

There are disturbing reports that results of randomized trials that showed clear beneficial effects have not been incorporated into practice after formal publication of the studies (Lancet 1993).

Results of the trial will be disseminated as widely as possible including publications and mass media efforts. To this end, the principal investigators in each study site and WHO collaborating centers will play a leading role. The recent experience of the Latin America Network of Reproductive and Perinatal Research (Langer, 1992), can be used as an example. Activities will include the following:

- (a) publication of the major finding in a mainstream journal, such as the New England Journal of Medicine or American Journal of Obstetrics and Gynecology;
- (b) publication of the major findings and editorials in regional that are published in local languages, such as Bulletin of PAHO (Spanish), Chinese, French or African journals;
- (c) publication of specialized and detailed articles in other peer reviewed journals such as (Clinical Trials", and in nursing and midwifery journals; methods and results of costing/cost effectiveness comparisons will be reported in health management and health economic literature such as "Health Economics", "Health Policy" and "Medical Care";
- (d) reports in the HRP and Safe Motherhood newsletters and other WHO publications;
- (e) publication of a trial newsletter "Maternal Care", with other relevant literature;
- (f) publication in periodicals from other collaborating institutions, such as Family Health International or Population Council;
- (g) presentation at local, regional and international meetings of obstetrics, nursing/midwifery, and public health;
- (h) ad hoc regional meeting of PIs and collaborators;
- (i) registration in the Oxford Database of Perinatal Trials or similar electronic systems;

- (j) publication by WHO of a book including all the collected information and detailed methodological issues unlikely to be included in reports to medical journals;

4.11.1 Authorship for publications in indexed journals

It is suggested that the so-called "modified conventional form" (Meinert, 1993) be used for the publications of the trial. This form includes attribution to the investigators that were primarily responsible for the trial followed by the name of the corporate research group: e.g. Ann A. Meyeis, Henry C. Brown,....., for the Antenatal Care Trial Research Group.

The list of investigator primarily responsible for the study will be prepared by the Steering Committee and should include only those actively involved in the preparation, organization, implementation of the trial as well as coordinating data analysis and manuscript preparation.

The order of authorship in individual papers will be decided by the Group. Credits will be given to the other participants of the trial such as associated staff at participating centers and key committee membership and will be listed at the end of the manuscript. Acknowledgements will be expressed in a footnote to the title or in a section following the credits. WHO/HRP certificate of collaboration will be given to doctors, midwives, nurses, local staff who contributed to the trial but whose names do not appear in the main papers.

There will be a Publications Sub-Committee of the Trial Steering Committee. This Sub-Committee will be responsible for:

- preparing a list of tentative publications during 1996;
- reviewing all papers sent for publication;
- reviewing and authorization of secondary analysis proposed.

4.12 Role of WHO

It is planned the WHO/HQ will play the leading role in the implementation and coordination of this protocol. Assistance will come from WHO collaborating centers, the regional offices and a selected group of leading scientists acting as WHO advisers. The new antenatal care package represents a major departure from the presently recommended, at least theoretically, form of care. It is considered the goal to be achieved. Furthermore, as this model is carried out to patients attending private practices in most developing countries (even the poorest), the suggestion of a simpler model could be seen as offering "cheap medicine for the poor". This perception has limited the implementation of other progress in the past. Finally, the traditional model is strongly incorporated into the obstetric culture with large economical implications for providers, particularly those who work in both the private and public sector. It is expected, therefore, that physicians, specifically those at the referral centers, will be reluctant to adopt this new programme which reduces the number of visits and eliminates traditional, but unproven, elements. The randomized controlled study design could contribute (and has done so in the past) to the acceptance of a programme like the one proposed in this protocol.

Thus, as an internationally recognized health institution with excellent scientific credibility in all countries, WHO is in a unique situation to carry out this project. It also has an already stabilized system for the dissemination of results at the country level once the study is finished. Discussions at scientific meetings and site visits with leading obstetricians and public health officers support the argument that WHO is the ideal institution to implement a project such as this.

The combination of the two WHO divisions preparing this project is unique in field. The Special Programme for Research, Development and Research Training in Human Reproduction is a world leader in reproductive health research and has a solid track record of conducting large, complex randomized controlled trials. It also has a network of highly developed research institutions that have previously participated in multi-centre trials, which can be included in this project with a very short preparatory phase and low cost. The Division of Family Health and the Safe Motherhood Programme is also in an ideal situation to facilitate the implementation of the programme, but may be more importantly, to disseminate and incorporate the results of the study to the MCH structure of as many developing countries as possible. With the collaboration of leading scientists of the study committees, both divisions will be a strong force to incorporate these results into the general of practice of obstetrics and gynecology in developed countries as well.

The technical activities of the WHO/HQ coordinating group will be assisted (as during the preparation of the protocol) by the staff of the National Perinatal Epidemiology Unit, Oxford, UK (Mrs M. Mugford); the National Institute of Public Health, Oslo Norway (Dr Leiv Bakketeig); and the Centro Rosario de Estudios Perinatales, Rosario, Argentina (Dr G. Carroli). The Oxford Unit and the centre in Argentina are presently coordinating two large WHO-supported randomized trials for the treatment of eclampsia and retained placenta.

In terms of financial support, this project is funded by multiple sources. The large cost of the project makes it difficult to obtain funding from only one agency; the topic is very attractive to most of the agencies working in health issues in developing countries, and the direct activities at country level are important to local institutions and governments. Therefore, the financial support has been provided by a consortium of agencies interested in MCH issues, such as WHO, UNDP, UNFPA, SAREC and the World Bank. Negotiations are being carried

out at the present time (with The Population Council and NIH/NICHHD) to expand the contribution sources in order to complete the required budget.

4.13 Personnel to work on the project

A basic staff will be needed by the coordination group and at each site. However, because of differences among the health systems, salary scales, geographical location, cultural characteristics, and style of collaborating institutions, local adjustments are made to this basic team.

The following personnel will be required to ensure the efficient running of the trial:

(a) Coordinating group:

- J.Villar, Coordinator, perinatal-reproductive epidemiologist.
- O. Meirik, Epidemiologist.
- G. Piaggio, Statistician.
- S. Mehta, Epidemiologist.
- A. Donner, Senior Consultant Statistician.
- A. Langer, Responsible, "Quality of Care".
- M. Mugford; Consultant Health Economist.
- Programmer.
- Secretary.

(b) At each study site (six sites):

- Principal investigator.
- Field director.
- Data unit coordinator.

- Data entry clerk.
- Hospital coordinator.
- Hospital data clerk.

(c) At each antenatal care clinic (only intervention group):

- Clinic coordinator.

Coordinating Group

The study will be centrally coordinated from Geneva by the Coordinating Group of the WHO Special Programme of Research, Development and Research Training in Human Reproduction. The special programme has 20 years of experience conducting large multicentre trials in developing countries. It is widely recognized as one of the leading research institutions in the world in reproductive health research. It has a statistical and data processing unit that has managed and analyzed many large trials; this unit is also well recognized in the research community. It will provide programming, supervision and training support for the participating centers for data cleaning, entry and computer file preparation. It will also assist the coordinating group during the data analysis which will be centrally conducted in Geneva.

The coordinating unit is led by Jose Villar, a senior researcher with considerable experience in perinatal research, particularly the implementation of large multicentre studies in developing countries. He will be assisted by Dr. Olav Meirik, Chief, Epidemiology Research Unit of the WHO Special Programme of Research, Development and Research Training in Human Reproduction, who also has extensive experience in multilateral epidemiological studies in developing countries and by Dr. S. Mehta, Head, Research Unit, WHO Safe Motherhood Programme, a gynaecologist/epidemiologist also with extensive research experience in developing countries. The statistician of the study will be Dr. Gilda Piaggio,

who was previously senior statistician at the Institute of Nutrition of Central America and Panama (INCAP) where she was responsible for the statistical aspects of large prospective field studies in Central America. She will be supported by the other statisticians of HRP and Dr. Allan Donner, Professor and Chairman, Department of Epidemiology and Biostatistics, University of Western Ontario, Canada and the leading expert in issues related to Cluster Randomization. Mrs. Miranda Mugford, a Health Economist at the National Perinatal Epidemiology Unit, Oxford University, U.K. is responsible for the economical evaluation of the trial, and Dr. Ana Langer, Senior Representative of the Population Council is responsible for the "Quality of Care" evaluation of the intervention.

The trial committees is shows is Appendix IV.

4.14 Time table

December 1994

- Finalize study protocol: contents, design of data collection forms.
- Recruit study centres.
- Complete funding negotiations.

February 1995

- Final operations manual and form adjustments.
- Pilot project in one or more centres.

September 1995

- Steering Committee Meeting.

November 1995

- Start preparatory activities - December 15, 1995, report of preparatory activities.

December 1995

- Thailand, Cuba, Saudi Arabia ready for randomization

March 1, 1996

- All clinics will be recruiting patients

October 1997

- Recruitment of subjects ends

October 1997 - April 1998

- End of follow-up period.

May - December 1998

- Preparation of Final Data set.
- Data analysis.
- Writing of report and manuscript(s).

4.15 Ethical issues

There are two main ethical issues related to the proposed trial: the first is the issue of reducing the number and content of antenatal visits from the standard, well-accepted antenatal care system as is recommended at the present time; the second is related to the mechanisms to obtain the informed consent of the participating women.

In relation to the first, we do not think there are violations of the rights of women for the following reasons:

- (a) The content and timing of visits presently recommended for normal, health pregnant women have not been scientifically evaluated, and relate mainly to traditional practice and some economical considerations. Two major international groups have extensively reviewed the situation in the USA and Europe, and have recommended the need for a systematic evaluation of prenatal care (Rosen, 1991; Lindmark, 1991). Furthermore, as discussed in sections 5 and 6.4 of the protocol, some of the present practices, such as routine ultrasound measures, measure of biparietal diameter with ultrasound after 20 weeks for gestational age dating, glucose tolerance test for screening for gestational diabetes, and measuring hemoglobin at every antenatal visit, have been demonstrated to be of limited value (Chalmers, 1989). Some practices may even be harmful (maternal weight restriction or routine vaginal examination). A recent comprehensive review of antenatal care stated that "visits that are not meaningful are counter-productive" (Rosen, 1991). We are proposing to include in the programme only those activities proven or strongly suggested to be beneficial to women and their babies (U.S. Public Health Service Expert Panel, 1989; Petitti et al., 1991).
- (b) Most women attending prenatal care in public clinics in developing countries do not receive, nor will they in the near future, the traditional "recommended" antenatal care programme. Present care is unevenly distributed, haphazardly allocated, and the visit length is clearly insufficient. The new system should allow health care providers to devote more time to the activities which are proven effective.

- (c) Medical conditions present before pregnancy or related to pregnancy will be referred and treated as presently recommended by local obstetrical practice for high risk patients.
- (d) Those study sites that currently offer activities know to be useful (e.g. alpha fetoprotein screening), but are not recommended in the basic package for logistic, economical or legal reasons, will continue performing those tests or procedures on all patients, regardless of randomization status.
- (e) There are currently large randomized controlled trials evaluating alternative forms of care for eclampsia or preventive interventions such as low-dose aspirin and calcium supplementation. In the event that results are available during the trial, the recommendations will be included in the antenatal care programme of both arms of the trial.

In reference to the informed consent, we are proposing that it be requested only from patients attending the antenatal clinics randomized to the new package (Hemminki, 1989; Zelen, 1979). Women attending the control clinics will receive the "best standard treatment" as presently offered in those clinics. Furthermore, because of the cluster allocation, informed consent of patients in the control group is not required, because data will be used no differently from the routine use of aggregate data by clinical departments for analysis of outcome information (Zelen, 1992).

Patients refusing to participate in the new programme will be offered the routine care at the same clinic or referred to the closest prenatal care clinic not included in the control group, but which offers the standard antenatal care for public institutions if the latter option is more convenient to the mother. Nevertheless, these patients will be included during the analysis in

the intervention clinics as originally randomized. The percentage of patients refusing the new programme will be used as process variables during the analysis. "Treatment" groups will continue with the same "treatment" to new patients during the follow-up of the last cohort of women enrolled in the study (about 6 months).

4.1.6 Implementation of the study in Khon Kaen, Thailand

The ethical approval was obtained from both the Ethics Committee of the Faculty of Medicine, Khon Kaen University and the Ethics Committee of the Ministry of Public Health, Thailand.

The principal investigator approached the chief medical officer of Khon Kaen province and obtained a permission to conduct this study in Khon Kaen province. The deputy-chief medical officer was assigned to be a co-investigator of the study.

The directors and the chiefs of health promotion division of the twelve biggest community hospitals in Khon Kaen were invited to attend a meeting. Names and some characteristics of these 12 hospitals are shown in Table 1. The investigator team presented a rationale, objectives, and detailed methodology of the trial. All twelve district hospital directors agreed to participate in the trial, keeping in mind that their hospitals would be randomly assigned into either the new antenatal care model or the traditional antenatal care scheme.

Before randomization a baseline survey was conducted to assess the availability of antenatal care services in these 12 district hospitals. Information was obtained by interviewing responsible health personnel and directly observed the ANC services by 4 supervisor nurses and reviewing the medical records of 64 subjects from each district hospital. Forms used in this survey are included in Appendix II.

Random allocation of the participating hospital was done centrally at WHO in Geneva.

Two workshops were organized for the preparation of involved personnel from all 12 district hospitals. The first workshop was for persons responsible for data collection. The rationale and objectives of the study were explained. Every item in all forms including Subject Number list, Classifying form (for intervention group only), Antenatal Hospital Admission form and Summary form was explained in detail. Examples were given for practice with all forms. Each hospital was provided with a manual of operation as a reference for questions arise later on. Adequate time was allowed for questions and clarification. Telephone and facsimile numbers were provided for future consultation.

A second workshop was organized for technicians from all 12 district hospitals involved in the trial. Procedures for hemoglobin measurement and VDRL assessment were described and demonstrated by a faculty member from Faculty of Associated Medical Science, Khon Kaen University. All participants practiced the laboratory procedures including hemoglobin determination and VDRL assessment under the supervision of the faculties. This was to ensure the standardization of the laboratory tests included in the study.

A third workshop was specially organized for responsible persons from 6 intervention hospitals. The philosophy of the new antenatal care model was explained to the directors of the 6 hospitals and the personnel responsible for providing antenatal care. The timing and contents of the 4 visits in the new antenatal care model were described in details. A checklist of intervention to be completed in each of the four visits was introduced to ensure a good compliance to a new antenatal care model. This checklist was incorporated into the medical record and is shown in Appendix I. Strong emphasis was clearly made that in this new antenatal care model women are the centre of activities. Adequate time should be allocated for providing relevant health education and allowing pregnant women and their relatives to ask questions.

Contact details of the principal investigators and coinvestigators were provided should they have any uncertainties or questions about the interventions or how to complete forms.

Recruitment started in all 12 district hospitals participated in the study on May 1, 1996 and continued for one year. All women coming for their antenatal care in these 12 hospitals during this one year period were recruited into the study regardless of their gestational age or risk status. Verbally informed consents were obtained only from pregnant women attending their antenatal care in the 6 intervention hospitals. Women who didn't consent for the new antenatal care model were requested to have their antenatal care at the nearby health centers or hospitals. All recruited women were followed up for their pregnancy outcomes. The follow up period extended for another 6 months after recruitment stopped.

Subject number list forms were used to record names and some information of every subject recruited into the study. Classifying forms were used to classify women only in the intervention hospitals into low and high risk groups. Low risk women received new basic antenatal care scheme. High risk women were managed according to the recommended treatment in that hospital or referred to a higher level of care. Antenatal hospital admission forms were completed for women admitted to the hospital for various conditions before delivery. Summary forms were completed for all women recruited into the study regardless of their pregnancy outcomes.

Principal investigators or coinvestigators or field coordinators visited these 12 hospitals fortnightly during the first 3 months and once a month for the rest of the 12 month recruitment and 6 month follow up period. This was to ensure a good quality recruitment, follow up and data collection procedure.

Responsible persons in each hospital were requested to send all forms (subject number list, classifying forms (in intervention hospitals), antenatal hospital admission and summary forms) monthly to the provincial health office where the field coordinators checked the actual number of forms received with the number indicated in the batch cover form. All forms were transferred from the provincial health office to the data coordinating unit at the Faculty of Medicine, Khon Kaen University. Data were doubly entered using the SPSS/DMS2 program provided by the Special Programme of Research, Development and Research Training in Human Reproduction, The World Health Organization, Geneva, Switzerland. Data were checked by various checking mechanisms. Query sheets were produced and sent to respective hospitals by facsimile. Update of the data was performed when response was obtained from hospitals. Data were transferred monthly to the central coordinating unit in Geneva via electronic mail. Summary forms for maternal deaths, fetal deaths and eclampsia cases had to be faxed to the coordinating unit in Khon Kaen University as soon as possible. These forms were then transferred to the central coordinating unit in Geneva also by fax. Number of these adverse outcomes by arms of the trial were reported periodically to the data safety monitoring committee only.

Mechanism was set up in these 12 hospitals and the other 4 referral hospitals in Khon Kaen to capture women who didn't deliver their babies in the hospital where they had their antenatal care. Summary forms were completed by responsible persons in the hospitals where deliveries took place and sent to the provincial health office with a notification to the original hospital of antenatal care.

Responsible persons in each hospital were also requested to monitor the expected date of delivery of each woman which was available in the subject number list. Any women who didn't show up for delivery within 2 weeks after the expected date of delivery were searched by various searching mechanisms including home visit. This was to minimize missing subjects.

Two meetings at about 3 and 6 months after starting recruitment were organized for all responsible persons from all 12 hospitals. This was to reinforce the good clinical practice principles. It also allowed sharing experiences and clarifying various issues.

5. RESULTS

Since the study in Thailand is a part of the multicenter WHO study the final evaluation of the new antenatal care model requires a combination of subjects from the 4 study sites to reach a targeted sample size. This report presents only descriptive data combining subjects from both the intervention and control groups.

5.1 Results of the baseline survey

As mentioned in the methodology part the baseline survey was conducted before randomization of the 12 district hospitals. The following information were obtained.

5.1.1 Clinical and laboratory activities

The mean working time for antenatal care services was 10.1 hours per week. All ANC clinics were operated by health promotion staff of the district hospitals. These were general practitioner and professional nurses but no specialists in obstetrics and gynecology. Five education and information activities were available in each clinic, Table 8.

Basic ANC activities were carried out for each pregnant woman. A vaginal examination was performed only in high risk cases. External version for breech presentation was not carried out. A formal risk score classification was not available. The screening laboratory tests and interventions that should be offered to all women were hemoglobin, blood test for syphilis, tetanus immunization and iron-folic acid supplementation. Only 3 clinics offered Rhesus antibody tests and none offered Pap smears and UTI screening. Most of the tests and interventions that should be offered to high risk cases were available except iodine supplements, colposcopic examination and alpha-feto protein determination, Table 9.

Laboratory tests for infectious diseases were performed in high risk cases. Test for hepatitis B were performed routinely in 3 clinics. No testing facilities for toxoplasmosis were available even in high risk cases, Table 10.

5.1.2 Characteristics of pregnant women

Characteristics of pregnant women are shown in Table 11. The average age and height of the women were 24.2 years and 154.4 centimeters respectively. The average gestational age at the first visit was 15 weeks. The average number of completed years of school was 6.6. Most subjects were married. There were 57.2% of the women with previous pregnancies and 53.3% of the women were parous. The prevalence of history of stillbirths, low birth weight and pre-eclampsia were 2.1%, 4.6% and 0.3% respectively.

5.1.3 Use of the services

Most of the basic ANC activities, including a dental examination were received by almost all pregnant women. Vaginal examinations were very infrequently carried out. Similarly, formal risk scores were infrequently made, Table 12.

More than 90% of the women had a syphilis antibody test, iron-folic acid supplementation and tetanus immunization. About a quarter (26.3%) of women were tested for Rhesus antibodies, but none had Pap smears or screening for UTI. Blood test for HIV antibodies and hepatitis B were done in 47.8% and 27.1% respectively. Few women, even those at risk had ultrasound scans, Table 13.

Every district hospital used the Ministry of Public Health MCH booklets. Only 62.9% of the records had maternal weight in the form of a Body Mass Index (BMI) graph. The

uterine height chart was not used. The lactation recommendation rate was high because of the implementation of the breast feeding campaign in Thailand. Although family planning is generally successful in Thailand, the contraception recommendation rate was only 57.8%. The percentage of women who received preconceptional counselling was also low, Table 14.

Only 4.8% of women made their first visit to an ANC clinic during the first trimester. The estimated mean cumulative number of ANC visits calculated by linear regression analysis at 30, 37 and 42 weeks of gestational age were 3.5, 6.4 and 8.1, respectively, Table 15.

5.2 Results of the main study

A total of 6765 subjects were recruited, 3449 subjects in the intervention group and 3316 subjects in the control group. Among the 3449 subjects in the intervention group, 3379 summary forms were completed, giving a 2.0% missing rate. The missing rate in the control group was 3.4% and the overall missing rate was 2.7%, Table 16.

The subject status is summarised in Table 17. There were 23 non-pregnant subjects, 182 subjects with abortion, 8 maternal deaths, 100 fetal deaths and 42 neonatal deaths.

5.2.1 Sociodemographic information

Most of the subjects (98.9%) were either married (48.2%) or stable union (50.7%), Table 18.

There were 18.7% teenage pregnancy and 4.6% elderly pregnancy, Table 19.

Majority (82.3%) of the subjects completed only primary education, Table 20.

There were very few subjects who smoked or used known substance abuse.

5.2.2 Obstetric history

About 40.7% of the subjects were primigravida, while 46.7% were primipara. Among multiparous subjects 3.3% had a history of previous stillbirth or neonatal loss and 8.7% had a history of low birth weight. Among 3379 subjects in the intervention group, only 6 (0.2%) had Rh negative blood group, Table 21.

5.2.3 Antenatal care

About 35.9% and 50.4% of the subjects started their antenatal care in the first and second trimester respectively, Table 22.

Median number of total ANC visits in the intervention and control groups were 4 (range 1-14) and 7 (range 1-20) respectively. In the intervention group, median number of visits to the original clinic, to other clinic and to high risk clinic were 3, 3 and 1 respectively. The corresponding figures in the control group were 5, 4 and 1 respectively, Table 23.

A high rate of completed tetanus immunization (90.5%) was achieved among these subjects. Most subjects (95.7%) had received iron supplementation. There were 144 (2.3%) subjects referred to a higher level of care. The 2 most common indications were uterine height low for gestational age and vaginal bleeding. There were 180 antenatal hospital admissions. The 3 most common indications were vaginal bleeding, preterm labor and urinary tract infection.

5.2.4 Maternal events during pregnancy

There were 59 subjects (0.9%) with hypertensive disorders of pregnancy. Among these, 4 were eclampsia cases, Table 24.

There were 189 (3.0%) subjects experiencing urinary tract infections during pregnancy, 84 subjects required antibiotic treatment and 29 subjects were admitted to the hospital.

Vaginal bleeding was reported by 136 (2.1%) subjects. There were 65, 33 and 38 subjects in the first, second and third trimester respectively.

The prevalence of anemia during pregnancy using WHO criterion (hemoglobin less than 110 g/l) was 25.9% (2643 subjects). There were 296 (4.7%) subjects with severe anemia (hemoglobin less than 90 g/l), Table 25.

Two hundred and sixty eight subjects had sexually transmitted diseases requiring treatment. Among these, 14 (0.2%) had syphilis.

Prelabour rupture of membranes occurred in 327 (5.2%) subjects.

5.2.5 Labour and delivery

Labour occurred spontaneously in 5932 (93.4%) subjects. The induction of labour and elective cesarean section rates were 3.9% and 2.6% respectively. Main indications for labour induction were postterm pregnancy and prelabour rupture of membranes.

Spontaneous delivery were achieved in 5739 (89.7%) subjects. The overall cesarean section rate was 6.4% (3.1% elective and 3.3% intrapartum). There were 241 vaginally operative deliveries (3.7%), Table 26. Main indications for cesarean section were cephalopelvic disproportion, previous cesarean section, breech or malpresentation and failure to progress.

The stillbirth rate was 1.5% (93 births), 45 (0.7%) were fresh stillbirth while 48 (0.8%) were macerated stillbirths.

The incidence of low birth weight was 9.0% (578 births). There were 97 babies weighing more than 4000 grams, Table 27.

The preterm delivery rate was 8.4% (541 births) and the postterm delivery rate (more than 42 weeks) was 7.0%, Table 28.

The incidence of severe birth asphyxia (Apgar score < 5) at one and five minutes after birth were 2.5% and 1.8% respectively. The incidence of mild birth asphyxia (Apgar score 5-7) at one and five minutes after birth were 4.5% and 0.6% respectively.

5.2.6 Postpartum information

The prevalence of postpartum anemia (hemoglobin less than 110 g/l) was 22.9% (1858 subjects). There were 403(6.3%) subjects with severe anemia, Table 29.

There were 23 subjects with a positive syphilis test after delivery. Among these 23 subjects, only 8 were treated in the antenatal period. Fifteen subjects were firstly diagnosed in the postpartum period.

There were 8 maternal deaths. The details of these deaths are described in Table 30. Three mothers died because of underlying medical conditions. Three mothers died due to condition mainly associated with delivery, namely postpartum hemorrhage, sepsis and amniotic fluid embolism. Causes for the other 2 deaths were not known.

5.2.7 Primary outcomes

The overall incidence of **maternal morbidity indicator index** (which was defined as the presence of at least one of the following condition, severe hypertension, preeclampsia, eclampsia, severe postpartum anemia and severe urinary tract infections or pyelonephritis) was 8.3%.

The overall incidence of **low birth weight** (less than 2500 g) was 9.0%.

5.2.8 Vital statistics

Table 31 shows the overall vital statistics. Fetal deaths (100 cases) contributes about 70% of the total perinatal deaths. The 3 most common causes of neonatal deaths were congenital malformation, preterm delivery and respiratory distress syndrome and birth asphyxia.

6. DISCUSSION

We have successfully recruited adequate number of subjects for this multicenter WHO study with a very good follow up. There were only 2.7% missing subjects. This was possible because of the very strong commitment from people in various institutions involved in this very important study.

We present in this report only the overall descriptive data, combining both intervention and control groups. We haven't attempted to compare the outcomes between the new and the traditional models of antenatal care. The statistical comparison should be done only all the data from the other 3 sites are available and combined. This analysis is expected to be done by the central coordination unit in Geneva in early 1999 and the result available in late 1999.

From this study we obtained the following maternal indicators, the maternal mortality rate of 122 per 100000 pregnant women, which was about 3 times the ratio reported by Department of Health, Ministry of Public Health, Thailand, 1997. Medically related and pregnancy and delivery related conditions contributed equally for the causes of maternal death. The rate of anemia in pregnant women was 25.9% compared to 12.9% reported by Ministry of Public Health also in 1997. The maternal morbidity indicator index was 8.3% and the abortion rate was 2.8%.

Concerning the perinatal indicators, the fetal death rate was 15.6 per 1000 total birth, the neonatal death rate was 6.7 per 1000 live birth, giving a perinatal mortality rate of 22.2 per 1000 total births. All these 3 rates are higher than those corresponding rates reported by Department of Health, Ministry of Public Health, Thailand, 1997. The low birth weight rate was 9.0% compared to 8.1% reported by Ministry of Public Health in 1995.

One significant finding from this study was about rate of syphilis infection. There were 23 patients with positive syphilis test after delivery. Only 8 of these 23 patients were diagnosed as having syphilis and were treated during pregnancy. The other 15 patients had a negative syphilis test and had not received any treatment during pregnancy. We are investigating in more details about the recommendation of a second test for syphilis in the third trimester of pregnancy using the information from this study.

The other interesting finding was the very low prevalence (0.2%) of Rh negative among Thai women. The cost benefit of implementing Rh determination as a routine screening procedure should be further evaluated.

The overall cesarean section rate was 6.4%. This already included all the referred cases. This rate was very low compared to the frightening national rate of 22.4% recently reported by the Health System Research Institute, Ministry of Public Health of Thailand.

Median number of antenatal care visits in the intervention group was 4 compared to the corresponding figure of 7 in the control group. This figure indicates a reasonably good protocol compliance to the number of visit in the intervention group. The median number of visits in the control group was very similar to the finding in the baseline survey.

The study conducted here in Thailand is an example of the excellent collaboration between academic institutions namely department of obstetrics and gynecology in the university and the health promotion center, Department of Health, Ministry of Public Health and the policy maker and implementation unit, the provincial health office.

The involvement of the department of health and the provincial health office, Ministry of Public Health will give a better chance of accepting this new antenatal care model in the future by the Ministry of Public Health should the result shows better clinical or economic or satisfaction outcomes.

We look forward to having the results of the complete trial comparing the clinical outcomes, cost and satisfaction between the new and the traditional antenatal care models.

7. ACKNOWLEDGEMENT

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Table 8 : Number of hospitals* with availability of human resources, education and information activities.

	No. of hospitals
Human resources	
General practitioner	12
Professional nurse	12
Administrative staff	12
Midwife	6
Laboratory technician	6
Obstetrician and Gynecologist	0
Ultrasonographer	0
Education and information activities	
Recommendation for lactation	12
Antenatal classes	12
Recommendation for contraception	12
Activities to reduce smoking	12
Preconceptional counselling	11

* Total number of hospitals = 12

Table 9 : Number of hospitals* offering screening, laboratory test and interventions.

Screening and laboratory test and interventions	No. of hospitals
Test or intervention that should be offered to all women	
Hemoglobin	12
Syphilis antibody	12
Tetanus toxoid	12
Iron-folic acid	12
Rhesus antibodies	3
Pap smear	0
UTI Screening	0
Test or intervention that should be offered to high risk women	
Pregnancy test	12
Glucose tolerance test	12
Ultrasonographic scanning	12
HIV antibodies	12
Nutrition supplement	12
Antibiotics	12
Iodine	4
Colposcopy	0
Alpha-feto protein	0

* Total number of hospitals = 12

Table 10 : Number of hospitals* offering screening, laboratory test for infectious diseases.

Screening and laboratory tests	No. of hospitals	
Hepatitis B	Low risk 3	High risk 12
Trichomoniasis	Low risk 0	High risk 12
Gonococcal investigation	Low risk 0	High risk 12
Malaria blood smear	Low risk 0	High risk 12
Toxoplasmosis	Low risk 0	High risk 0

* Total number of hospitals = 12

Table 11 : Characteristics of pregnant women.

Characteristics	Total number = 768		
	Number	Mean	95% CI
Age (years)	766	24.2	23.8 - 24.6
Height (cms)	739	154.4	153.9 - 154.8
Gestational age at 1st visit (weeks)	753	15	14.4 - 15.5
Number of completed years of school	408	6.6	6.3 - 6.9
Number of persons by room	32	2.2	1.9 - 2.5
	Number	%	95% CI
Marital status	766	99.8	99.8 - 100.0
Previous pregnancy	445	57.2	53.4 - 61.1
Parous	409	53.3	49.5 - 57.2
Stillbirths	14	2.1	0.8 - 3.3
Low birth weight babies	36	4.6	2.9 - 6.3
Pre-eclampsia/Eclampsia	2	0.3	0.0 - 0.7
History of Obst-Gyne surgery	3	0.4	0.0 - 0.9
Tetanus immunization	753	98.1	97.2 - 99.1
Iron supplementation	754	98.2	97.3 - 99.2
Treated for Trichomoniasis	3	0.4	0.0 - 0.9
Treated for syphilis	2	0.3	0.0 - 0.6
Treated for other STD	0	0	-

Table 12 : Actual clinical activities received by pregnant women.

Clinical activities	Total number = 768	
	%	95% CI
Physical examination	99.8	99.4 - 100
Routine Obstetric examination	99.3	98.7 - 99.8
Uterine height measurement	99.0	98.2 - 99.8
Breast examination	98.6	97.8 - 99.5
Blood pressure measurement	96.7	95.0 - 98.3
Dental examination	95.1	93.6 - 96.6
Maternal weight gain monitoring	73.5*	72.1 - 74.9
Vaginal examination	0.8	0.1 - 1.6
Formal risk score classification	0.8	0.1 - 1.5

* About 26.5% were first visits, therefore maternal weight gain monitoring was not applicable.

Table 13 : Actual screening and laboratory tests received by pregnant women.

Screening and laboratory tests and interventions that should be offered to all women	Total number = 768	
	%	95% CI
Syphilis antibody	97.9	96.9 - 99.0
Iron-folic acid level	95.1	93.4 - 96.8
Tetanus toxoid	92.0	90.0 - 93.9
Rhesus antibodies	26.3	25.7 - 26.9
Pap smear	0.0	-
UTI screening	0.0	-
Screening and laboratory tests and interventions that should be offered to high risk women	%	95% CI
HIV antibodies	47.8	45.2 - 50.4
Pregnancy test	12.8	10.7 - 14.9
Nutrition supplement	2.8	1.6 - 4.0
Alpha-feto protein	0.0	-
Ultrasonographic scanning	0.0	-
Screening and laboratory tests for infectious diseases	%	95% CI
Hepatitis B	27.1	26.1 - 28.0
Gonococcal	0.2	0.0 - 0.5
Trichomoniasis/yeast	0.0	0.0 - 0.6
Malaria	0.0	-
Toxoplasmosis	0.0	-

Table 14 : Actual use of instruments, health education and information activities and human resources.

Instruments	Total number = 768	
	%	95% CI
Maternal weight gain chart	62.9	61.5 - 64.3
Doppler for fetal heart	31.1	28.8 - 33.3
Vaginal speculum	0.4	0.0 - 0.9
Uterine height chart	0.0	-
Education and information activities		
Recommendation for lactation	97.8	96.8 - 98.7
Antenatal classes	83.4	82.5 - 84.2
Recommendation for contraception	57.8	55.6 - 60.1
Activities to reduce smoking	14.6	13.6 - 15.5
Preconceptional counseling	8.5	6.4 - 10.7
Human resources		
Professional nurse	98.4	97.5 - 99.3
Obstetrician and Gynecologist	0.0	-
General practitioner	0.0	-

Table 15 : Number of ANC visits by linear regression analysis

Gestational age (weeks)	No. of women	No. of visits	95% CI
30	518	3.5	3.3 - 3.7
37	167	6.4	5.9 - 6.9
42	76	8.1	6.0 - 10.2

Table 16 : Forms Processed

Clinics/Hospitals	No. Recruited Subjects	No. of CLA forms	No. Summary forms	% Missing SUM forms
Chumpae	1064	1064	1030	3.2%
Banphai	759	759	754	0.7%
Phol	594	594	579	2.5%
Nonsonghong	493	493	491	0.4%
Khaosunakwang	320	320	315	1.6%
Waeng Noi	219	219	210	4.1%
Intervention	3449	3449	3379	2.0%
Kranuan	859		854	0.6%
Manjakiri	342		336	1.8%
Nongrua	674		654	3.0%
Phuwiang	449		413	8.0%
Srichompoo	630		613	2.7%
Nampong	362		334	7.7%
Control	3316		3204	3.4%
All Clinics/Hospitals	6765		6583	2.7%

Table 17 : Subject status

Status	Number	%
Total recruited subjects	6765	100.0%
Summary forms available	6583	97.3%
Not pregnant	23	0.3%
Abortion	182	2.8%
Maternal death	8	0.1%
Fetal death	100	1.4%
Neonatal death	42	0.6%
Moved away	24	0.3%

Table 18 : Marital status

Marital status	Number	%
Single	30	0.5
Married	3163	48.2
Stable union	3327	50.7
Separated	24	0.4
Divorced	8	0.1
Widowed	8	0.1
Total	6560	100.0

Table 19 : Maternal age at first visit

Age (years)	Number	%
less than 19	1225	18.7
20 - 34	5032	76.7
more than 35	303	4.6
Total	6560	100.0

Table 20 : Number of years in school

Years in school	Number	%
0 to 6	5400	82.3
7 to 12	999	15.2
more than 12	155	2.4
Total	6554	100.0

Table 21 : Obstetric history

Obstetric history	Number	%
Primigravida	2667	40.7
Primipara	3062	46.7
No. of previous stillbirth or neonatal loss	126	3.3
History of low birth weight	337	8.7
Iso-immunization (Rh -ve)	6	0.2

Table 22 : Gestational age at first visit

Gestational age at first visit (weeks)	Number	%
less than 12	2354	35.9
12 - 28	3306	50.4
more than 28	894	13.6
missing	6	0.1
Total	6560	100.0

Table 23 : Median number of ANC visits

Group	Original clinic	Other clinic	High risk clinic
Intervention	3 (1-12)	3 (1-12)	1 (1-5)
Control	5 (1-17)	4 (1-12)	1 (1-9)

Table 24 : Hypertensive disorders of pregnancy

	Number	%
Hypertension	32	0.5
Hypertension with treatment	2	0.0
Pre-eclampsia	9	0.1
Pre-eclampsia admitted to hospital	12	0.2
Eclampsia	4	0.1
No	6295	99.1
Total	6354	100.0

Table 25 : Hemoglobin concentration during pregnancy

Hemoglobin concentration (g/l)	Number	%
less than 90	296	4.7
90 - 110	1347	21.2
more than 110	4697	73.9
missing	14	0.2
Total	6354	100.0

Table 26 : Mode of delivery

Mode of delivery	Number	%
Spontaneous	5739	89.7
Elective cesarean	199	3.1
Intrapartum cesarean	210	3.3
Vacuum extraction	95	1.5
Forceps extraction	92	1.4
Assisted breech	54	0.8
Missing	10	0.1
Total	6399	100.0

Table 27 : Birth weight

Birth weight (grams)	Number	%
less than 1000	31	0.5
1000 - 2499	547	8.6
2500 - 4000	5687	88.8
more than 4000	97	1.5
missing	37	0.6
Total	6399	100.0

Table 28 : Gestational age at birth

Gestational age at birth (weeks)	Number	%
less than 28	52	0.8
28 - 36	489	7.6
37 - 41	5418	84.7
> 42	422	7.0
missing	18	0.3
Total	6399	100.0

Table 29 : Hemoglobin value in postpartum period

Hb concentration (g/l)	Number	%
less than 90	403	6.3
90 to 110	1455	22.9
more than 110	4137	65.1
missing	359	5.7
Total	6354	100.0

Table 30 : Maternal death

	Hospital	Study No	Name	Age	Parity	Date of death	Place of death	Cause
1.	06	0162-D	N.T.	26	1	05/09/96	NongSongHong Hospital	PPH
2.	12	0100-B	T.C.	44	3	18/12/96	Khon Kaen Hospital	Diabetic nephropathy
3.	01	0365-F	K.C.	30	1	09/01/97	Chumpae Hospital	Pulmonary edema Thyrotoxicosis
4.	09	0214-F	P.M.	35	0	26/02/97	Home	Unknown
5.	07	0529-X	S.J.	27	1	25/08/97	Home	Tuberculous meningitis
6.	09	0457-F	N.Y.	34	4	06/09/97	Death before arrival	Unknown
7.	01	1019-L	T.P.	26	1	11/10/97	Khon Kaen Hospital	Sepsis
8.	08	0427-C	J.S.	22	0	02/01/98	Khon Kaen Hospital	Amniotic fluid embolism

Table 31 : Vital statistics

1. Maternal death rate	8/6536	=	0.122%
2. Abortion rate	182/6536	=	2.785%
3. Fetal death rate	100/6399	=	1.562%
4. Neonatal death rate	42/6299	=	0.667%
5. Perinatal death rate	142/6399	=	2.219%

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APPENDIX I : DATA COLLECTION FORMS

WHO/HRP - Clinical Trial Management System

--- SUBJECT NUMBER LIST ---

Project : 95915 Antenatal Clinical Trial

Clinic : 2 KRANUAN

Subject No	Date Assigned	Name / Address	Clinic Recore Number	Informed Consent	Estimated date of Delivery	Date of Post- partum Visit	Trans- ferred
0001-L/...../...../...../.....
0002-P/...../...../...../.....
0003-T/...../...../...../.....
0004-W/...../...../...../.....
0005-Z/...../...../...../.....
0006-C/...../...../...../.....
0007-F/...../...../...../.....
0008-J/...../...../...../.....
0009-M/...../...../...../.....
0010-N/...../...../...../.....
0011-T/...../...../...../.....
0012-X/...../...../...../.....
0013-B/...../...../...../.....
0014-F/...../...../...../.....
0015-K/...../...../...../.....

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IDENTIFICATION	
(a) Form code	S U M
(b) HRP Study number	9 5 9 1 5
(c) Study site	
(d) Clinic code	
(e) Subject number	
(f) Hospital record number	
(g) Clinic record number	

PERSONAL DATA OF MOTHER	
1. Marital status	<input type="checkbox"/>
1 = single	
2 = married	
3 = stable union	
4 = separated	
5 = divorced	
6 = widowed	
2. Age at last birthday at the first antenatal visit	Years <input type="checkbox"/>
3. Number of completed years in school	<input type="checkbox"/>
4. a) Number of persons in household	<input type="checkbox"/>
b) Number of rooms	<input type="checkbox"/>
5. Smoking	<input type="checkbox"/>
1 = Never	
2 = Yes, but not during this pregnancy	
3 = Smoked during this pregnancy	
6. Known 'substance' abuse (including heavy alcohol drinking)	<input type="checkbox"/>
1 = No 2 = Yes	
7. Maternal height	cm <input type="checkbox"/>
8. Maternal weight at the first visit	kg <input type="checkbox"/>

OBSTETRIC HISTORY	
9. Number of pregnancies INCLUDING current pregnancy	<input type="checkbox"/>
10. Number of previous births EXCLUDING current delivery	<input type="checkbox"/>

11. Number of previous stillbirth or neonatal losses	<input type="checkbox"/>
12. Number of abortions	<input type="checkbox"/>
13. a) Number of babies birthweight < 2500 g	<input type="checkbox"/>
b) Number of babies birthweight > 4500 g	<input type="checkbox"/>
14. Outcome of immediately previous pregnancy	<input type="checkbox"/>
1 = Abortion	
2 = Stillbirth	
3 = Livebirth, birthweight = or > 2500 g	
4 = Livebirth, birthweight < 2500 g	
5 = Neonatal death	
6 = Other	
15. Hospital admission in last pregnancy for hypertension or pre-eclampsia/eclampsia	<input type="checkbox"/>
1 = No 2 = Yes	
16. Any previous surgery on reproductive tract? (Myomectomy, removal of septum, cone biopsy, classical CS, cervical cerclage)	<input type="checkbox"/>
1 = No 2 = Yes	
17. Iso-immunization Rh(-) in current or in previous pregnancy	<input type="checkbox"/>
1 = No 2 = Yes	

ANTENATAL CARE	
18. First day of the last normal menstrual period	day month year <input type="checkbox"/>
19. Date of first antenatal visit	day month year <input type="checkbox"/>
20. Visits to antenatal care or hospital outpatient clinics	Gestational age
a) 1st visit	Completed weeks <input type="checkbox"/>
b) 2nd visit	<input type="checkbox"/>
c) 3rd visit	<input type="checkbox"/>
d) 4th visit	<input type="checkbox"/>
e) 5th visit	<input type="checkbox"/>
21. Total number of visits:	
a) to the original antenatal care clinic	<input type="checkbox"/>
b) to any other antenatal clinic	<input type="checkbox"/>
c) to a hospital high risk clinic	<input type="checkbox"/>

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Subject number

Grid for subject number

22. Tetanus immunization

- 1 = No
2 = Incomplete (1 dose)
3 = Yes (complete 2 doses)
4 = Previously immunized (1 dose)

23. a) Iron supplementation

- 1 = No 2 = Yes
3 = Contraindicated

b) If Yes, gestational age when supplementation started Weeks

24. a) Referred to higher level of antenatal care

- 1 = No 2 = Yes

If No, go to Q 26

1st 2nd

b) If Yes, gestational age at referral

Grid for gestational age at referral

25. Principal reason for referral

- 1 = No 2 = Yes

- a) Pregnancy induced hypertension
b) Pre-eclampsia
c) Severe anaemia (< 70 g/l)
d) Chronic hypertension
e) Uterine height low for gestational age
f) Malpresentation or breech
g) Multiple gestation
h) Pyelonephritis or urinary infection
i) Vaginal bleeding
j) Diabetes mellitus
k) Cardiac disease
l) Chronic respiratory conditions
m) Renal disease
n) Pelvic mass
o) Isoimmunization Rh(-)
p) Other

Grid for principal reason for referral (1st and 2nd)

26. After referral, the mother

- 1 = Continued care at higher level of antenatal care
2 = Was referred back to the original antenatal care clinic (or level)
3 = Was scheduled for hospital admission (complete Form 2 - AHA)

Grid for referral outcome (1st and 2nd)

27. Any hospital admission during the antenatal period

- 1 = No 2 = Yes

MATERNAL EVENTS DURING PREGNANCY

28. Hypertensive disorders of pregnancy

- 1 = No 2 = Yes

- a) Only hypertension, no treatment
b) Only hypertension with treatment or referral
c) Pre-eclampsia (hypertension and proteinuria)
d) Pre-eclampsia admitted to hospital
e) Eclampsia

29. Urinary tract infection

- 1 = No
2 = Yes, no treatment
3 = Yes, with antibiotic treatment
4 = Yes, with hospital admission

30. Vaginal bleeding during pregnancy

- 1 = No 2 = Yes

- a) First trimester
b) Second trimester
c) Third trimester

31. Lowest haemoglobin value during pregnancy g/l

Grid for lowest haemoglobin value

32. Was the mother treated for any of the following conditions during pregnancy?

- 1 = No 2 = Yes

- a) Trichomoniasis, moniliasis or any other abnormal discharge
b) Syphilis
c) Any other sexually transmitted diseases

33. Was external version for breech or malpresentation attempted?

- 1 = No, cephalic presentation
2 = Breech or malpresentation, no version attempted
3 = Version attempted

34. Prelabour rupture of membranes

- 1 = No 2 = Yes

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Subject number

Grid for subject number

LABOUR AND DELIVERY

35. At admission in labour, did the mother have any of the following conditions?
1 = No
2 = Yes, noted during antenatal period
3 = Yes, first noted at admission

- a) Pregnancy induced hypertension
b) Pre-eclampsia
c) Severe anaemia (< 70 g/l)
d) Chronic hypertension
e) Uterine height low for gestational age
f) Malpresentation or breech
g) Multiple gestation
h) Pyelonephritis or urinary infection
i) Vaginal bleeding
j) Diabetes mellitus
k) Cardiac disease
l) Chronic respiratory conditions
m) Renal disease
n) Pelvic mass
o) Isoimmunization Rh(-)
p) Other

36. Fetal heart rate present at admission in labour
1 = No 2 = Yes

37. Onset of labour
1 = Spontaneous
2 = Induction (Complete Question 38)
3 = Elective caesarean section

38. Indications for induction of labour
1 = No 2 = Yes

- a) Prelabour rupture of membranes
b) Post-term
c) Intrauterine growth retardation
d) Chronic fetal distress
e) Pre-eclampsia
f) Maternal medical complications
g) Pregnancy complications
h) Isoimmunization Rh(-)

POSTPARTUM INFORMATION

39. Lowest haemoglobin value g/l

Grid for haemoglobin value

40. Syphilis test
1 = Negative 2 = Positive

Grid for syphilis test

41. a) Maternal death
1 = No 2 = Yes
b) If Yes, cause of death

Grid for maternal death

ICD-10 code

42. Date of mother's discharge from hospital or death

Grid for date of discharge

NEONATAL OUTCOME

43. Date of delivery or abortion

Grid for date of delivery

44. Time of delivery

Grid for time of delivery

45. Total number of fetuses

Grid for total number of fetuses

If more than 1 fetus, please fill additional Summary form, completing Identification and Neonatal Outcome (Q43 - Q60)

46. Birth order (if multiple delivery)

Grid for birth order

47. Mode of delivery

- 1 = Spontaneous
2 = Elective caesarean section (Complete Question 48)
3 = Intrapartum caesarean section (Complete Question 48)
4 = Vacuum
5 = Forceps
6 = Assisted breech or breech extraction
7 = Internal version and extraction

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Subject number

Grid for subject number

48. If caesarean section, indications

1 = No 2 = Yes

- a) Fetal distress
b) Failure to progress
c) Breech or other malpresentation
d) Maternal medical complications
e) Pregnancy complications
f) Previous caesarean section
g) Multiple pregnancy
h) Cephalopelvic disproportion
i) Intrauterine growth retardation
j) Other

Vertical grid for caesarean section indications

49. Fetal presentation at delivery

1 = Cephalic
2 = Breech
3 = Other

Grid for fetal presentation

50. Status at birth:

1 = Live birth
2 = Fresh stillbirth
3 = Macerated stillbirth

Grid for status at birth

51. Birthweight

g Grid for birthweight

52. Infant sex

1 = Male
2 = Female

Grid for infant sex

53. Gestational age at birth or abortion (best obstetric estimate) Completed weeks

Grid for gestational age

54. Apgar score

- a) at 1 minute
b) at 5 minutes

Grid for Apgar scores

55. a) Any congenital malformations?

1 = No 2 = Yes

b) If Yes, specify ICD-10 code

56. a) Admission of the newborn to Intensive Care Unit or any special care unit

1 = No 2 = Yes

b) If Yes, specify the principal reason

ICD-10 code

c) If Yes, specify the number of days in Intensive Care Unit or any special care unit

Grid for number of days

57. a) Newborn status at discharge

1 = Alive
2 = Dead
3 = Referred to another hospital or unit

Grid for newborn status

b) If dead, cause of death

ICD-10 code

58. a) If referred to another hospital or unit, status at 7th day of life

1 = Alive
2 = Dead

Grid for status at 7th day

b) If dead, cause of death

ICD-10 code

59. Date of newborn's discharge from hospital or death

Grid for date (day, month, year)

60. If dead, time of death

Grid for time of death (hour, minute)

REMARKS

Large text area for remarks

Hospital code

Grid for hospital code

Recorder number

Grid for recorder number

Signature

Date

BASIC ANTENATAL CARE CHECKLIST

CHECK THE ACTIVITIES CARRIED OUT WHERE APPROPRIATE (UNSHADED BOXES)

Use the closest gestational age at the time of visit

Patient's Name _____ Clinic Record No. _____ Study Subject No. ____/____/____/____

FIRST VISIT for all women at first contact with clinics, regardless of gestational age. If first visit later than recommended, carry out all activities up to that time DATE: / /	Visits			
	1st <12 wks	2nd	3rd	4th
Classifying Form indicates eligibility for the basic programme				
Clinical examination				
Clinically severe anemia: Hb test				
Ob exam : gestational age estimation, uterine height				
Gyn exam (can be postponed until second visit)				
Blood pressure				
Maternal weight / height				
Rapid syphilis test, detection of symptomatic STDs - treatment				
Urine test (multiple dipstick)				
Blood type and Rh				
Tetanus toxoid				
Fe / Folic acid supplementation				
Recommendation for emergencies / hot line for emergencies				
Complete antenatal card				
SECOND VISIT and SUBSEQUENT VISITS DATE: / /	<i>Gestational age - approx. # of weeks:</i> 26 32 38			
Clinical examination for anemia				
Ob exam: gestational age estimation, uterine height, fetal heart rate				
Blood pressure				
Maternal weight (only women with low weight at first visit)				
Urine test for protein (only nulliparous/women with previous eclampsia)				
Fe / Folic acid supplementation				
Recommendation for emergencies				
Complete antenatal card				
THIRD VISIT: add DATE: / /				
Hemoglobin				
Tetanus toxoid (second dose)				
Instructions for delivery				
Recommendations for lactation / contraception				
FOURTH VISIT: add DATE: / /				
Detection of breech presentation & referral for external version				
Complete ANC card, recommend it be brought to hospital				

Staff responsible for antenatal care: Name _____

Batch Cover Form

To be Completed by the Investigator

Clinic Name

Clinic/Hospital number

Name and Signature of Investigator

Date batch sent

Summary of Batch Contents

Form name	No of forms
CLA	
SUM	
AHA	
MUL	

To be Completed By Coordinating Centre

Batch Number Allocated

Date batch received

Date batch processed

Date Query sheet produced

Remarks

APPENDIX II : ANTENATAL CARE CONTENT SURVEY FORMS



STUDY 95915 - ANTENATAL CARE TRIAL
ANTENATAL CARE CONTENT SURVEY - CLINIC LEVEL

CLINIC

Page 1

IDENTIFICATION

Name and address of the clinic

1 Study site

2 Clinic code

3 Clinic location

- 1 = urban
- 2 = peri-urban
- 3 = rural
- 4 = other _____

4 This clinic belongs to:

- 1 = Municipal government
- 2 = Provincial government
- 3 = Ministry of Health
- 4 = University system
- 5 = Other _____

5 This clinic is:

- 1 = a free standing clinic for mother and children only
- 2 = part of a clinic with several other specialties
- 3 = part of a small hospital
- 4 = part of a large maternity hospital
- 5 = part of a referral, secondary or tertiary level hospital
- 6 = other _____

6 This clinic is open for antenatal visits

a) number of days per week

b) number of hours per working day

7 Number of NEW antenatal care patients per month

8 Percentage of NEW antenatal care patients per month considered as high risk %

Please check in the corresponding box the activities, tests or interventions which are provided in this clinic as a part of the antenatal care programme to all pregnant women or only to some (high risk) women or in a referral clinic or hospital.
 Do not complete shaded boxes.

ACTIVITY	Available/done at the clinic		Available/done only in a hospital or referral clinic belonging to the same health system		Not available/done in this health care system
	All women	High risk women only	All women	High risk women only	
CLINICAL ACTIVITIES					
TICK ONE BOX ONLY					
9 Medical history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10 Educational history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11 Socioeconomic history	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12 Physical examination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13 Formal risk score classification	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14 Obstetrical examination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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STUDY 95915 - ANTENATAL CARE TRIAL
ANTENATAL CARE CONTENT SURVEY - CLINIC LEVEL

CLINIC

Page 2

ACTIVITY	Available/done at the clinic		Available/done only in a hospital or referral clinic belonging to the same health system		Not available/done in this health care system
	All women	High risk women only	All women	High risk women only	
TICK ONE BOX ONLY					
15 Uterine height measure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16 Vaginal examination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17 Evaluation of pelvic size	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18 Breast examination	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19 Maternal weight	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20 Maternal weight gain monitoring	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21 Maternal height	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22 Blood pressure measurement	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23 External version	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
24 Other <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25 Other <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

DENTAL EXAMINATION	TICK ONE BOX ONLY				
26 Formal dental examination	<input type="checkbox"/>				

SCREENING AND CLINICAL LABORATORY TESTS	TICK ONE BOX ONLY				
27 Pregnancy test	<input type="checkbox"/>				
28 Rhesus antibodies/ABO	<input type="checkbox"/>				
29 Hepatitis B	<input type="checkbox"/>				
30 Toxoplasmosis	<input type="checkbox"/>				
31 Alpha-feto protein	<input type="checkbox"/>				
32 Oral glucose test	<input type="checkbox"/>				
33 Glucose tolerance test (full)	<input type="checkbox"/>				

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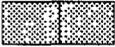


STUDY 95915 - ANTENATAL CARE TRIAL

CLINIC

ANTENATAL CARE CONTENT SURVEY - CLINIC LEVEL

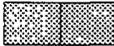
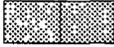
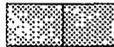
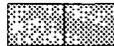
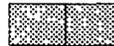
Page 3

ACTIVITY	Available/done at the clinic		Available/done only in a hospital or referral clinic belonging to the same health system		Not available/done in this health care system
	All women	High risk women only	All women	High risk women only	
TICK ONE BOX ONLY					
34 Pap smear	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35 Colposcopy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36 Ultrasonographic scanning	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
37 Haemoglobin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
38 Haematocrit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
39 Serum ferritin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
40 Fasting blood glucose test	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
41 Syphilis antibody	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
42 HIV antibody	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
43 Malaria blood smear	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
44 Gonococcal investigation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
45 Trichomoniasis/yeast	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
46 Bacterial culture of urine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
47 Urine dipstick	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
48 Other _____ 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
49 Other _____ 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PREVENTIVE OR THERAPEUTIC INTERVENTIONS OFFERED FREE OF CHARGE	TICK ONE BOX ONLY				
50 Tetanus toxoid	<input type="checkbox"/>				
51 Iron - folic acid	<input type="checkbox"/>				

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ACTIVITY	Available/done at the clinic		Available/done only in a hospital or referral clinic belonging to the same health system		Not available/done in this health care system
	All women	High risk women only	All women	High risk women only	
TICK ONE BOX ONLY					
52 Nutrition supplementation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
53 Other vitamins - minerals a) If available in this clinic, specify type	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____ 					
54 Antibiotics a) If available in this clinic, specify types	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____ 					
_____ 					
55 Other _____ 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TICK ONE BOX ONLY					
EQUIPMENT AND INSTRUMENTS					
56 Adult weighing scales	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
57 Sphygmomanometer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
58 Uterine height chart	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
59 Maternal weight gain chart	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
60 Vaginal speculum	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
61 Hand held Doppler for fetal heart rate a) If Yes, specify type	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____ 					
62 Pinnal/Fetal stethoscope	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
63 Ultrasound a) If Yes, specify type	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____ 					
64 Cardiotocograph a) If Yes, specify type	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____ 					
65 Gravidogram for gestational	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



STUDY 95915 - ANTENATAL CARE TRIAL
 ANTENATAL CARE CONTENT SURVEY - CLINIC LEVEL

CLINIC

Page 5

ACTIVITY	Available/done at the clinic		Available/done only in a hospital or referral clinic belonging to the same health system		Not available/done in this health care system
	All women	High risk women only	All women	High risk women only	
TICK ONE BOX ONLY					
66 Perinatal medical record pre-coded for computer use	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
67 Referral form to higher level of care using a formal risk score	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
68 Scheduled visits for routine care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
69 Continuity of care (same MD or midwife follows the same patient)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
70 Other _____ 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
71 Other _____ 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

OTHER RESOURCES IN THE SAME BUILDING	TICK ONE BOX ONLY				
72 High risk clinic	<input type="checkbox"/>				
73 High risk beds	<input type="checkbox"/>				
74 Delivery beds	<input type="checkbox"/>				
75 Independent antenatal consultation rooms a) If available in this clinic, specify number of rooms <input type="text"/> <input type="text"/>	<input type="checkbox"/>				
76 Independent dressing rooms a) If available in this clinic, specify number of rooms <input type="text"/> <input type="text"/>	<input type="checkbox"/>				
77 Other medical clinics for referral of patients	<input type="checkbox"/>				
78 Other _____ 	<input type="checkbox"/>				
Other _____ 	<input type="checkbox"/>				

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STUDY 95915 - ANTENATAL CARE TRIAL
 ANTENATAL CARE CONTENT SURVEY - CLINIC LEVEL

CLINIC

Page 6

ACTIVITY	If available in this clinic, specify the number	Available in this clinic	Available only in a hospital or referral clinic belonging to the same health system	Not available in this health care system
HUMAN RESOURCES PER CLINIC SESSION	Number	TICK ONE BOX ONLY		
79 Specialist in Obs/Gyn.	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
80 General practitioner	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
81 Midwife	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
82 Professional nurse	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
83 Empirical nurse	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
84 Biochemist	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
85 Laboratory technician	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
86 Ultrasonographer	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
87 Clerical/administrative staff	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
88 Other <input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
89 Other <input type="checkbox"/>	<input type="text"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

EDUCATION-INFORMATION	TICK ONE BOX ONLY		
90 Preconceptional counseling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
91 Antenatal classes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
92 Education for future parents	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
93 Activities to reduce smoking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
94 Recommendation for lactation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
95 Recommendation for contraception	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
96 Other <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Date form completed

<input type="text"/>					
day		month		year	

Recorder's name

100



STUDY 95915 - ANTENATAL CARE TRIAL
 ANTENATAL CARE CONTENT SURVEY - PATIENT LEVEL

PATIENT

Page 1

a) Study number

9 5 9 1 5

b) Study site

c) Clinic code

d) Survey subject number

Please extract the following information from the Clinical Record.
 If the information is not available, use 9, 99 or 999. Do not complete shaded boxes.

1 Clinic record number

2 Date of last visit

day month year

3 Gestational age at the last visit

weeks

4 Number of antenatal visits so far in this pregnancy

5 Marital status

- 1 = Single
- 2 = Married
- 3 = Stable union
- 4 = Separated
- 5 = Divorced
- 6 = Widowed

6 Age at last birthday

years

7 Number of completed years in school

8 a) Number of persons in household

b) Number of rooms in the house

9 Number of pregnancies INCLUDING current pregnancy

10 Number of live births

11 Number of stillbirths or neonatal losses (< 28 days postnatal)

12 Number of babies with birthweight < 2500g

13 Hospital admission in the last pregnancy for hypertension or pre-eclampsia/eclampsia

- 1 = No 2 = Yes
- 8 = Not applicable

14 Any previous gynaecological/obstetrical surgery?

- 1 = No 2 = Yes

15 First day of the last normal menstrual period

day month year

16 Date of first antenatal visit

day month year

17 Height

cm

18 Weight at the first visit

kg

19 Lowest haemoglobin value recorded in this pregnancy

g/l

20 Tetanus immunization

- 1 = No 2 = Yes

21 Iron supplementation

- 1 = No 2 = Yes

22 Was the mother treated for any of the following conditions during pregnancy?

- 1 = No 2 = Yes

a) Trichomoniasis, moniliasis or any other abnormal vaginal discharge

b) Syphilis

c) Any other sexually transmitted diseases

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STUDY 95915 - ANTENATAL CARE TRIAL
ANTENATAL CARE CONTENT SURVEY - PATIENT LEVEL

PATIENT

Page 2

Survey subject number _____

Please check in the corresponding boxes the activities, tests or interventions which were provided to this patient at this clinic

CLINICAL ACTIVITIES

PERFORMED

	LAST VISIT		ANY PREVIOUS VISIT
23 Physical examination	<input type="checkbox"/>		<input type="checkbox"/>
24 Formal risk score classification	<input type="checkbox"/>		<input type="checkbox"/>
25 Obstetrical examination	<input type="checkbox"/>		<input type="checkbox"/>
26 Uterine height measure	<input type="checkbox"/>		<input type="checkbox"/>
27 Vaginal examination	<input type="checkbox"/>		<input type="checkbox"/>
28 Breast examination	<input type="checkbox"/>		<input type="checkbox"/>
29 Maternal weight gain monitoring	<input type="checkbox"/>		<input type="checkbox"/>
30 Blood pressure measurement	<input type="checkbox"/>		<input type="checkbox"/>
31 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>
32 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>

DENTAL EXAMINATION

PERFORMED

	LAST VISIT		ANY PREVIOUS VISIT
33 Formal dental examination	<input type="checkbox"/>		<input type="checkbox"/>

SCREENING AND CLINICAL LABORATORY TESTS

PERFORMED

	LAST VISIT		ANY PREVIOUS VISIT
34 Pregnancy test	<input type="checkbox"/>		<input type="checkbox"/>
35 Rhesus antibodies/ABO	<input type="checkbox"/>		<input type="checkbox"/>
36 Hepatitis B	<input type="checkbox"/>		<input type="checkbox"/>
37 Toxoplasmosis	<input type="checkbox"/>		<input type="checkbox"/>
38 Alpha-feto protein	<input type="checkbox"/>		<input type="checkbox"/>
39 Fasting blood glucose test	<input type="checkbox"/>		<input type="checkbox"/>
40 Oral glucose test	<input type="checkbox"/>		<input type="checkbox"/>
41 Pap smear	<input type="checkbox"/>		<input type="checkbox"/>



STUDY 95915 - ANTENATAL CARE TRIAL

PATIENT

ANTENATAL CARE CONTENT SURVEY - PATIENT LEVEL

Page 3

Survey subject number

Please check in the corresponding boxes the activities, tests or interventions which were provided to this patient at this clinic.

PERFORMED

	LAST VISIT		ANY PREVIOUS VISIT
42 Haematocrit	<input type="checkbox"/>		<input type="checkbox"/>
43 Syphilis antibody	<input type="checkbox"/>		<input type="checkbox"/>
44 HIV antibody	<input type="checkbox"/>		<input type="checkbox"/>
45 Malaria blood smear	<input type="checkbox"/>		<input type="checkbox"/>
46 Gonococcal investigation	<input type="checkbox"/>		<input type="checkbox"/>
47 Trichomoniasis/yeast	<input type="checkbox"/>		<input type="checkbox"/>
48 Bacterial culture of urine	<input type="checkbox"/>		<input type="checkbox"/>
49 Urine dipstick	<input type="checkbox"/>		<input type="checkbox"/>
50 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>
51 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>

PREVENTIVE OR THERAPEUTIC INTERVENTIONS

	LAST VISIT	GIVEN	ANY PREVIOUS VISIT
52 Tetanus toxoid	<input type="checkbox"/>		<input type="checkbox"/>
53 Iron - folic acid	<input type="checkbox"/>		<input type="checkbox"/>
54 Nutrition supplementation	<input type="checkbox"/>		<input type="checkbox"/>
55 Calcium supplementation	<input type="checkbox"/>		<input type="checkbox"/>
56 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>
57 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>

EQUIPMENT AND INSTRUMENTS

	LAST VISIT	USED/DONE	ANY PREVIOUS VISIT
58 Uterine height chart	<input type="checkbox"/>		<input type="checkbox"/>
59 Maternal weight gain chart	<input type="checkbox"/>		<input type="checkbox"/>
60 Vaginal speculum	<input type="checkbox"/>		<input type="checkbox"/>
61 Doppler for fetal heart rate	<input type="checkbox"/>		<input type="checkbox"/>
62 Ultrasound	<input type="checkbox"/>		<input type="checkbox"/>
63 Other, specify _____	<input type="checkbox"/>		<input type="checkbox"/>

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STUDY 95915 - ANTENATAL CARE TRIAL

PATIENT

ANTENATAL CARE CONTENT SURVEY - PATIENT LEVEL

Page 4

Survey subject number

Please check in the corresponding boxes the activities, tests or interventions which were provided to this patient at this clinic

EDUCATION-INFORMATION

PROVIDED

- 65 Preconceptional counseling
- 66 Antenatal classes - Education of expectant parents
- 67 Activities to reduce smoking
- 68 Recommendation for contraception
- 69 Recommendation for lactation

HUMAN RESOURCES

70 Primary provider of Antenatal Care (tick one box only)

- a) Specialist in Obstetrics/Gynaecology
- b) General practitioner
- c) Midwife
- d) Professional nurse
- e) Empirical nurse
- f) Other

If other is marked, specify

71 Continuity of care (same MD or midwife follows the same patient)

72 Scheduled visits for routine antenatal care

73 Advice for the subsequent visit:

- a) Planned scheduled routine antenatal visit
- b) Referred

If Yes, specify where to:

Date form completed

day month year

Recorder's name

Signature

Position

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APPENDIX III : DUMMY TABLES FOR THE ANALYSIS

Table I: NUMBER OF TRIAL PARTICIPANTS

Country	Intervention		Control	
	Cluster	Number of Pregnancies	Cluster	Number of Pregnancies
1. Thailand	1		1	
	2		2	
	:		:	
	:		:	
	m_1		m_1	
2. Cuba	1		1	
	2		2	
	:		:	
	:		:	
	m_2		m_2	
3. Argentina	1		1	
	2		2	
	:		:	
	:		:	
	m_3		m_3	
4. Saudi Arabia	1		1	
	2		2	
	:		:	
	:		:	
	m_4		m_4	
5. South Africa	1		1	
	2		2	
	:		:	
	:		:	
	m_5		m_5	

Table II: CLUSTER-LEVEL CHARACTERISTICS AT THE INITIATION OF TRIAL

	CLUSTER	
	Intervention	Control
	N =	N =
Number of new antenatal care patients per month X (SD)		
Cluster location (% rural)		
Delivery facilities at clinic (%)		
Antenatal care primarily provided by Obs/Gyn MD Midwife Nurse Other		
Equipment available		
Laboratory test performed at clinic		

Table III: CHARACTERISTICS OF WOMEN AT TRIAL ENTRY

	CLUSTERS	
	Intervention	Control
	(N=)	(N=)
Maternal age		
Maternal education (% < primary)		
Parity		
Smoking (%)		
Gestational age at randomization		
History of abnormal pregnancies (%)		
Clinical pathology (%)		
Married (%)		
Employed (%)		
Interval since last delivery <24 m (%)		
Previous C.S. (%)		
First visit weight (kg)		
Race or ethnicity (%)		
Previous LBW infant (%)		
Low SES %		
Clinical pathology (%)		

Table IV: DESCRIPTION OF THE TWO ANTENATAL CARE POLICIES

PRENATAL CARE ACTIVITIES	CLUSTERS		Differences in means or %
	Intervention	Control	
	(N=)	(N=)	(95% CI)
Total No. of prenatal visits			
Referrals to hospital by trimester (%)			
Number of measures of: maternal weight vaginal examinations blood pressure uterine height			
Number of urine tests			
External versions 3rd trimester (%)			
Complete tetanus toxoid (%)			
Prenatal visits with health ed. component (%)			
Receiving iron supplementation (%)			

NOTE: This Table will be completed with information from the routine antenatal care from the study sites.

Table V: PRIMARY OUTCOME BY "INTENTION TO TREAT"
FOR ALL WOMEN RANDOMIZED

	CLUSTERS		Relative Risk (95% CI)
	Intervention	Control	
	(N=)	(N=)	
LBW (%)			
Maternal morbidity index (%)			

Table VI: SECONDARY OUTCOMES BY "INTENTION TO TREAT"
FOR ALL WOMEN RANDOMIZED

SECONDARY OUTCOMES	CLUSTERS		Relative Risk (95% CI)
	Intervention	Control	
Incidence of proteinuric ^(*) -pre-eclampsia or eclampsia			
Prevalence of post partum anemia (hemoglobin <90g/l) ^(**)			
Incidence of severe urinary tract infection/pyelonephritis (requiring antibiotic treatment ^(***) or hospitalization)			
Rate of treated syphilis and any other STDs			
Rate of post-partum positive syphilis test ^(***) (among women without treatment during pregnancy)			
Rate of incomplete tetanus immunization			
Rate of post partum hospital stay ≥7 days for maternal complications			
Rate of IUGR ^(#)			
Rate of preterm delivery (<37 weeks)			
Rate of spontaneous & PROM pre-term delivery : <35weeks : 35-36 weeks			
Rate of medically indicated pre-term delivery : <35 weeks : 35-36 weeks			
Rate of breech presentation at birth			
Rate of very LBW (<1500 g)			
Rate of Apgar score <5 at 5'			
Rate of I.C.U. stay > 2 days			
Rate of fetal death			
Rate of pre-discharge neonatal death			

* Proteinuria of 2.0 g or more in 24h or 2+ or more on qualitative examination (dipstick)

** Requires postpartum blood samples

*** Excluding the antibiotics given to treat asymptomatic bacteriuria

- Maternal morbidity indicator index: the presence of at least one of the following:

proteinuric-preeclampsia, eclampsia, severe hypertension (≥ 160/110 mmHg)(during pregnancy or within 24 h of delivery; post-partum anemia (<90 g/l); severe urinary tract infection/pyelonephritis (requiring antibiotic treatment or hospitalization)

If LNMP not available, use the best "obstetric" estimation; below 10th percentile of international standard

Table VII: PERINATAL DEATHS BY "INTENTION TO TREAT"
AND BY ANTENATAL CARE PROGRAMME

PERINATAL DEATH BY AGE AT DEATH	CLUSTERS		Relative risk (95% CI)
	Intervention	Control	
	(N=	(N=)	
Fetal deaths:			
Fresh stillbirth			
Macerated stillbirth			
Neonatal deaths:			
0 - 6 days			
7 - 27 days			

Table VIII: MATERNAL DEATHS BY "INTENTION TO TREAT"
AND BY ANTENATAL CARE PROGRAMME

MATERNAL DEATHS BY TIME OF DEATH	CLUSTERS		Relative risk (95% CI)
	Intervention	Control	
	(N=)	(N=)	
During pregnancy			
During labour and delivery			
Post partum			

Table IX: ADVERSE PREGNANCY OUTCOMES BY "INTENTION TO TREAT"
AND BY ANTENATAL CARE PROGRAMME

	CLUSTERS		Relative risk (95% CI)
	Intervention	Control	
	(N=)	(N=)	
Undiagnosed multiple pregnancies (%)			
Undiagnosed grossly IUGR (%)			
Severe anemia (<90g/l) at birth (%)			
Undiagnosed malpresentations at start of labour (%)			
Eclampsia (%)			
Untreated malaria (%)			
Untreated syphilis (%)			
Untreated other infections (i.e. tuberculosis) (%)			

APPENDIX IV : TRIAL COMMITTEES

TRIAL COMMITTEES

Coordinating Unit

Dr. Jose Villar, Trial Coordinator

Dr. Olav Meirik, Epidemiologist, HRP/WHO

Dr. Gilda Piaggio, Statistician, HRP/WHO

Dr. Suman Mehta, Gynaecologist/Epidemiologist, FHE/WHO

Statistical Consultant

Allan Donner, Statistician, Canada

Steering Committee

1. Yagob al-Mazrou, Principal Investigator, Saudi Arabia
2. Leiv Bakketeig, Public Health Obstetrician, Norway
3. Jose M. Belizan, Principal Investigator, Argentina
4. Heinz Berendes, Epidemiologist, USA (Chairperson)
5. Ubaldo Farnot, Principal Investigator, Cuba
6. Ana Langer, Focal Personal, Quality of Care Evaluation, Mexico
7. Pisake Lumbiganon, Principal Investigator, Thailand
8. Sam Ross, Principal Investigator, South Africa
9. Miranda Mugford, Focal Person, Economic Evaluation, U.K.
10. Vivian Wong, Obstetrician/Gynaecologist, Hong Kong

Data and Safety monitoring Committee

1. Heinz Berendes, Epidemiologist, USA
2. Per Bergsjø, Obstetrician/Epidemiologist, Norway
3. Gerard Breart, Epidemiologist, France
4. Alfredo Morabia, Biostatistician/Epidemiologist, Switzerland
5. Gilda Piaggio, Statistician, WHO

Consultants

1. Hassan Ba'aqeel, Gynaecologist, Saudi Arabia
2. Guillermo Carroli, Randomized Trials, Obstetrician, Argentina
3. Gunilla Lindmark, Obstetrician, Sweden

Administrative and Secretarial Support

1. Mrs. Joyce Starks
2. Mrs. Brenda Curina