CLUSTER RANDOMIZED CONTROLLED TRIAL FOR IMPROVING PERINATAL CARE IN LATIN AMERICA

STUDY PROTOCOL

Latin American Center for Perinatology (CLAP)
Pan American Health Organization (PAHO)
World Health Organization (WHO)
Montevideo, Uruguay

Department of Maternal and Child Health
School of Public Health
The University of North Carolina at Chapel Hill
United States

Global Network for Women's and Children's Health Research
National Institute of Child Health and Human Development
National Institutes of Health
United States

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Abstract

Many obstetrical interventions used in Latin America, as in other parts of the world, have been shown to be ineffective or harmful, while effective interventions remain underutilized. The goal of this project is to develop and evaluate an intervention intended to implement evidence-based practices among birth attendants in Latin America.

The aim of this project is to perform a cluster randomized controlled trial of a behavioral intervention in Argentina and Uruguay that will increase the use of two evidence-based birth practices, the selective use of episiotomies and active management of the third stage of labor. The intervention will be based on the stages of change and organizational change theories and tailored by formative research that will include baseline questionnaires and focus groups.

Twenty-four hospitals in three urban districts of Argentina and Uruguay will be randomized. Opinion leaders in the 12 intervention hospitals will be identified and trained to develop evidence-based guidelines. They will then diffuse the guidelines by using a multifaceted approach including seminars, academic detailing, reminders, and feedback on utilization rates. The 12 hospitals in the nonintervention group will continue with their standard in-service training activities. The main outcomes to be assessed are the use of episiotomies and of oxytocin during the third stage of labor. Secondary outcomes will be perineal sutures, potspartum hemorrhages, and birth attendants' opinions.

The Latin American Center for Perinatology (CLAP) will be the coordinating center for the trial. In this way, the project endeavors to facilitate capacity building of CLAP and its network of hospitals to perform studies integrating behavioral and clinical research methods. It is also anticipated that the project will contribute to the Global Network by increasing access to a large number of Latin American hospitals that have the capacity to participate in multicentric randomized controlled trials and other clinical studies.

1. Study Objectives and Significance

1.1. Statement of the Problem

The evaluation of the medical care in general and of the area of perinatology in particular, shows alarming results. It has been seen that only 15% of the health related practices are based on valid scientific evidence. This situation is even more serious in Latin American countries, where a significant proportion of the care administered to women during the prenatal period, delivery, and the postpartum are scientifically verified as ineffective or harmful.

For example, Belizán et al. (1999), estimated that 12 of the 19 Latin American countries they examined had cesarean section rates above the maximum 15% rate recommended by the World Health Organization (WHO). They calculated that around 850,000 unnecessary cesarean sections are performed each year in the Latin American region. Additionally, many other obstetrical interventions used in Latin America, as in other parts of the world, are not evidence based.

Another practice that follows the same pattern is routine use of episiotomy a practice demonstrated as useless and even harmful (Carroli and Belizán, 2000). We studied the use of episiotomy in 41 hospitals in Latin America between 1990 and 1998. The range of episiotomy rates in vaginal births of nulliparous women is between 49.3% and 98.3%, the median rate is 91.3%, and the mean value is 88.4% (Althabe et al., 2002). From these figures, we can conclude that every 10 women giving birth vaginally for the first time, 9 are currently receiving an episiotomy. Simultaneously, many of the practices verified as beneficial are not routinely used. For example, the management of the third stage of labor has been proven to be beneficial for the prevention of postpartum hemorrhage. (Prendiville et al., 2000). However, a survey in 19 maternity services of Montevideo, Rosario, and Province of Buenos Aires showed that in 17 of them (89.5%), expectant management was the standard form of care.

Support during labor and delivery that is proven to be beneficial and with no undesirable effects was used in only 21% of women in the survey of the 19 hospitals mentioned above (Althabe and Belizan, 2001).

Although we have no figures, the administration of enemas at admission in labor, perineal shaving, and systematic intravenous infusion are other examples of practices not supported by scientific evidence that are still used in a wide proportion of Latin American hospitals. External cephalic version at term is another example of an evidence-based practice that is not used in Latin American hospitals.

The barriers to change

Why, despite scientific evidence and dissemination efforts are harmful and/or unnecessary procedures still used, while other beneficial procedures are ignored?

What are the bridges and barriers between practice guidelines based on research findings and practitioners? As a wide variety of barriers can hinder practitioners from adhering to

evidence-based practices, a theoretical framework could help explain these barriers and possibly help target interventions to specific barriers. Cabana et al. published a comprehensive systematic review about the barriers to physician adherence to practice guidelines and developed a theoretical approach to the barriers (Cabana et al., 1999).

They review 76 articles which include 5 qualitative studies and 120 different surveys asking questions regarding possible barriers to guideline adherence. Barriers could be classified into seven general categories: the barriers affecting physician knowledge (lack of awareness and lack of familiarity); those affecting attitudes (lack of agreement, lack of self-efficacy, lack of outcome expectancy and the inertia of previous practices); and those affecting behavior (external barriers).

One survey included in Cabana's review is related to the perinatal field and consisted in a survey of 38 childbirth-related organizations regarding the use of the text Effective Care in Pregnancy and Childbirth (Lomas, 1993). One of the aspects covered by the survey was the perception of which were the main barriers to effective research transfer. All organizations cited especially the practitioners' failure to keep up with the literature, the lack of resources, and the absence of appreciation for research information as major obstructions for implementation of research findings.

There is not much information regarding this issue in Latin American countries. At least in some countries, there is an active distrust towards change. In a recent study carried out in Argentina, for example, health workers expressed resistance and anger towards top-down programs that were imposed upon them (Pittman et al., 1998). This resentment builds on dissatisfaction with working conditions. In the same study, physicians linked their resistance to new programs to the drop in salary levels and the loss in the social status of their profession. As such, they saw themselves as victims of an unfair situation.

There is no relevant evidence that quantifies the relative weight of each one of the categoriesof barriers, mainly because most of the studies were done focusing on some of the barriers and not all of them. It is probable that the relative weight varies according to the specialty, specific problem addressed, and setting. We think that the differences among countries are referred to the relative weight of categories, more than to the existence of other general types of barriers.

1.2. Background

1.2.1. Interventions to change professional practice

Several trials have been performed in North America and Europe to evaluate strategies to change behaviors of birth attendants. Lomas et al. (1991) conducted a trial in Canada with 76 physicians to test three interventions to increase the number of vaginal births after C-section. The interventions compared were (1) distribution of educational materials, (2) local opinion leaders and distribution of educational materials, and (3) audit and feedback and distribution of educational materials. The use of opinion leaders was significantly more effective than audit and feedback and than educational materials alone in increasing the number of women offered a trial of labor and increasing the number of vaginal births.

Another trial performed in Canada (Hodnett et al., 1996) compared a strategy based on the influence of nurse opinion leaders to no intervention. It was hypothesized that the strategy would result in lower rates of epidural analgesia through increasing the amount of support nurses provided to their patients. Other outcomes included rates of narcotic analgesia, episiotomy, and operative delivery. The results showed that the strategy was unsuccessful in improving intrapartum nursing care. The individual marketing approach used in the intervention de-emphasized information about research and did not include institutional changes. The authors suggested that this might partly explain the lack of success of the intervention.

One trial comparing the introduction of a database of systematic reviews, the Cochrane Pregnancy & Childbirth Database, with a control group has been conducted recently (Wyatt et al., 1998). This trial has compared the introduction of the Cochrane database through a single educational visit (outreach visit) conducted by an expert obstetrician with a control group that did not receive any intervention. The educational visit involved meeting with the lead obstetrician and nurse of the labor ward and demonstrating how to select and interpret Cochrane reviews. Twenty-five obstetric units within a small geographic area in England were included in this trial. There was a significant increase in the use of only one of the four recommended practices (vacuum extraction). However, this trial has been conducted in a region where awareness of evidence-based medicine and Cochrane reviews increased significantly during the trial period in both the study and control hospitals, reducing the magnitude of any possible impact of the intervention.

Another cluster randomized trial performed in the United States evaluated the effect of an “active dissemination” strategy compared to a “usual dissemination” strategy, on the use of corticosteroids for fetal lung maturation prior to a preterm birth in 27 hospitals (Leviton et al., 1999). The active strategy consisted of the use of a local opinion leader, grand round lectures given by respected national experts, chart reminders, group interactive discussions, and audit and feed back. In usual dissemination hospitals, the use of corticosteroids increased from 33% to 58% or by 75% over baseline. The active dissemination hospitals increased from 33% to 68% or by 108% over baseline.

Very few trials of a similar nature have been performed in developing countries, and the results of the few that have been performed are inconclusive. Two trials utilizing educational outreach visits were conducted in Indonesia. Santoso et al. (1996) compared two interventions (outreach visits or a formal seminar) to a nonintervention control to improve drug use in the management of acute diarrhea in children. They reported that outreach visits resulted in a significant 24% relative reduction in antimicrobial use compared with the control group. There was a significant 40% relative reduction in the use of antidiarrheals compared to the control group. The authors also reported that the seminar resulted in significantly greater changes from the baseline period than did the outreach group. The use of oral rehydration agents was not significantly improved after either intervention (9% reduction). Ross-Degnan and colleagues (Ross-Degnan et al., 1996) reported that outreach visits to pharmacists/owners, coupled with a small group session with counter attendants, significantly increased sales of oral hydration salts by 40% and reduced antidiarrheal sales by 35% for the treatment of diarrhea.

In sum, multiple strategies to change medical behaviors have been used, with various degrees of success. Few trials have been done in obstetrical settings or in developing countries.

To our knowledge, no randomized controlled trial has been performed to evaluate the effectiveness of an intervention to implement evidence-based birth practices in Latin American countries.

1.2.2. An approach to obtain changes.

We consider that a behavioral intervention designed to

- increase birth attendant concern about the effectiveness of routine clinical practices,
- stimulate their desire to review the effectiveness of their practice,
- provide them with skills to perform evidence-based clinical guidelines appraisal and development, and
- establish mechanisms through key hospital leaders to implement the guidelines and sustain them over time,

will increase the use of evidence-based practices in Latin American countries.

Our proposal is based on the following assumptions:

(a) *Clinical guidelines may be used to enhance the quality of care provided to patients.*

Clinical guidelines are systematically developed recommendations, used to assist patients and professionals in decisions concerning the appropriate health care for specific clinical circumstances (Duggan and Cohen, 1998).

The utilization of scientifically valid clinical guidelines can facilitate more consistent, effective, and efficient health care that would lead to improvement of the health of the population.

A review of 59 controlled trials that evaluated the effect of the implementation of clinical guidelines on the process of health care showed that in 55 of them, the implementation of the guidelines generated positive changes in the medical behavior. In 9 of 11 of these studies in which morbidity outcomes were evaluated, the outcomes improved (Grimshaw et al., 1993).

In order to achieve these results, clinical guidelines should fulfill a careful systematic process of development, implementation, and maintenance. In the last decade, this process has had a great development of its methodological aspects, mainly in developed countries that follow strong evidence-based medicine criteria for the development of its health policies.

(b) *Clinical guidelines should be developed or critically appraised and adapted by clinicians.*

For that purpose, health professionals should learn to evaluate (critically appraise) medical literature. Clinicians should regularly consult the original literature and be able to

critically appraise the methods and results sections to solve clinical problems and provide optimal patient care.

The underlying belief is that physicians can gain the skills to make independent assessments of evidence and thus evaluate the credibility of opinions being offered by experts. In general, the new skills that are needed to sustain this approach are the following: (1) identify clinically relevant problems and formulate the problems as questions that can be answered; (2) define what information is required to solve the problems; (3) conduct an efficient search of the literature; (4) select the best of relevant studies by applying the rules of evidence to determine their validity; (5) be able to present, in a succinct fashion, the content of the article and its strengths and weaknesses; and (6) extract the clinical message and apply it to the clinical problem. One of the objectives of the proposed intervention is to implement a training strategy at the hospital level to teach these skills to birth attendants and opinion leaders in order to develop simple clinical guidelines.

(c) *The strategies to be used have to be based on methods likely to be effective in changing professional behavior.*

Many methods to change medical behavior have been developed and used in industrialized countries. A comprehensive review by Oxman et al. (1995) examined 102 studies of improving physician practices and concluded that there are no "magic bullets." They conclude that the best approach is to combine several strategies, such as the use of local opinion leaders, workshops, outreach visits (academic detailing), reminders, and audit and feedback. Other, more recent, reviews showed similar conclusions (Bero et al., 1998). Similarly, Grol (1997) states that no one method of changing practices is superior. He recommends using a stages-of-change/diffusion of innovations theoretical model. The steps include (a) develop the proposal based on sound evidence and/or consensus of opinion leaders, and present the proposal to credible groups in an attractive and easily accessible format; (b) identify barriers/obstacles to change; (c) link interventions to obstacles and different phases of the change process (different interventions may be needed for different target groups of clinicians); (d) develop the plan; and (e) carry out plan and evaluate progress.

(d) *The intervention should follow a theoretical framework of stages of change.*

The intervention should be based on a multilevel theoretical framework that tailors interventions according to the stage of change of the individual practitioner and the stage of diffusion of innovations at the hospital level.

The Stages of Change Transtheoretical Model (TTM) could serve as the theoretical basis for the intervention at the level of the individual birth attendants. The TTM is a particularly useful heuristic approach for understanding how people undergo the process of changing practices and behaviors and how interventions can best be designed to promote behavioral change (Prochaska et al.,1992). At the core of the model is the assumption that behavioral change is a dynamic process that involves several distinct stages. The stages include precontemplation (not considering changing one’s behavior), contemplation (thinking about changing), preparation (definitely planning to change and may have made preliminary attempts), action (has changed behavior in the short term, usually defined as within the past 6 months), and maintenance (continuing beyond 6

months) following initial change. Research in a number of health behavior areas indicates that different cognitive and behavioral factors are associated with movement through the stages (Prochaska et al., 1994). Practically, the model points to the need for different intervention strategies for individuals at different stages of the change process. For example, motivational information and confidence-enhancing messages and cues (such as chart prompts and reminders) may work best for individuals who are in the earlier contemplative stages of the process. Specific behavioral skill-training interventions and supportive normative environments, on the other hand, may be most effective for individuals in the later stages. Recent studies indicate that such tailored interventions are effective for promoting change in a variety of health behaviors (Skinner et al., 1999).

At the hospital level, the intervention should be based on the Diffusion of Innovations model and the Stage Theory of Organizational Change. Diffusion is defined as the process through which an innovation is communicated through channels over time among members of a social system (Rogers, 1983; Beyer and Trice, 1978). An innovation is an idea, practice, service, or object that is considered new by an individual or social group. According to diffusion theory, certain characteristics of innovations increase the chances that they will be widely adopted. Innovations are more likely to succeed if they are perceived as compatible with existing value systems and lifestyles. Despite the compatibility with the existing system, people tend to adopt innovations at different rates, and this phenomenon can be used to design interventions. The "early adopters" often are more highly educated and actively use information-seeking processes. Media sources (such as broadcast media, print materials, and the Internet) are effective in promoting awareness and interest in trying new things among the early adopters. Later adopters tend to be more influenced by interpersonal sources of communication, especially from respected individuals, opinion leaders, and peers, who can promote new health practices and programs among these groups (Rogers, 1983).

Research focused on organizational changes aimed at adopting innovative policies, programs, or practices shows that change typically occurs in a series of stages. The major stages include awareness, adoption, implementation, and institutionalisation (Beyer and Trice, 1978). Organizational development principles suggest that specially in the early stages, decisions regarding organizational change should be made by participation of all levels of health providers in the hospitals in identifying problems and their solutions (Sorensen et al., 1992; Strychker et al.,1997).

We developed an intervention following the previous considerations. Table 1 shows the correspondence between the theoretical models and the components of the intervention. It will use two obstetric practices (selective use of episiotomies and active management of the third stage of labor) as models for the implementation and evaluation of the experimental intervention.

Table 1: Correspondence between the theoretical models and the components of our intervention.

Intervention	TTM	Organizational Change
Presentation and selection of opinion leaders	Pre-contemplation	Awareness
Guidelines development	Contemplation (early adopters)	Awareness
Dissemination	Contemplation (late adopters); Preparation	Adoption
Implementation	Action	Implementation
Maintenance	Maintenance	Institutionalization

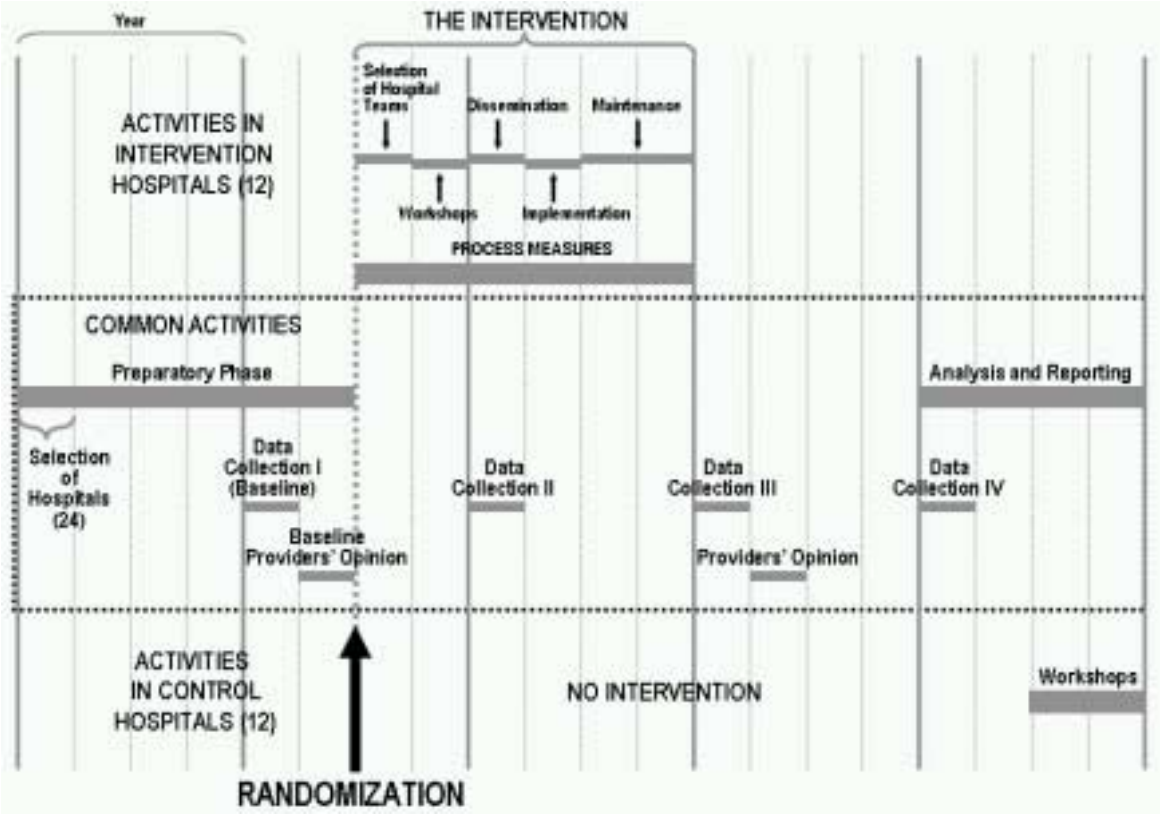
2. Study Design

2.1. Design

2.1.1. General outline

To achieve the objective of the behavioral intervention to increase the use of two evidence-based birth practices (selective use of episiotomies and active management of the third stage of labor) by birth attendants, we will randomize 24 hospitals in Argentina and Uruguay into intervention and control groups. The intervention will be based on the stages of change and organizational change theories and tailored by formative research. It will include identification and training of opinion leaders who will develop evidence-based guidelines and use a multifaceted approach to disseminate, implement, and maintain the guidelines. The approach will include seminars, academic detailing, reminders, and feedback on utilization rates. The 12 hospitals in the control group will continue with their standard in-service training activities. A preparatory phase will precede the intervention phase, and both phases will past 18 months. Figure 1 summarizes the design.

Figure 1. Study design.



2.2. Primary Hypotheses

Our main hypothesis is that an intervention designed to motivate and facilitate health care professionals' development through the implementation and maintenance of simple evidence-based guidelines can increase the use of evidence-based practices by birth attendants at the hospital level in Argentina and Uruguay.

The main specific aim of this project is to perform a randomized controlled trial of a behavioral intervention intended to increase the use of two evidence-based birth practices, the selective use of episiotomies and active management of the third stage of labor (injection 10 IU of oxytocin). We will randomize 24 hospitals in Department of Montevideo, Uruguay, the Province of Buenos Aires, Argentina, and the City of Rosario, Argentina.

The *main research questions* to test the main hypothesis are the following:

- Does the proposed intervention decrease the frequency of episiotomies (primary outcome) and of perineal sutures (secondary outcome) in the intervention hospitals relative to the control hospitals?
- Does the proposed intervention increase the frequency of injections of oxytocin during the third stage of labor (primary outcome), and decrease the frequency of postpartum hemorrhages (secondary outcome) in the intervention hospitals relative to the control hospitals?

Secondary research questions are the following*:*

- Does the proposed intervention increase the readiness to change of birth attendants (secondary outcome) in the intervention hospitals relative to the control hospitals?
- Are the effects, if any, sustained 1 year after the end of the intervention?

Our *other aims* are to do the following:

Facilitate capacity building within the Latin American Center for Perinatology (CLAP: Centro Latinoamericano de Perinatologia) and among its network of hospitals, so that they may increase their ability to perform studies integrating behavioral and clinical research methods, and to perform large scale studies using state-of-the-art information technology.

Contribute to the Global Network by increasing access to a large number of Latin American hospitals that have the capacity to participate in multicentric randomized controlled trials and other clinical studies.

2.3. Primary outcomes

- Episiotomy rate among single vaginal deliveries.
- Rate of injection of 10 I.U. of oxytocin during third stage of labor in single vaginal deliveries.

2.4. Secondary outcomes

2.4.1. Clinical secondary outcomes

- Perineal sutures rate among single vaginal deliveries.
- Incidence of postpartum hemorrhage >500ml among single vaginal deliveries.

Perineal sutures and hemorrhages will be studied to estimate the health impact of the intervention. Previous studies have established that selective use of episiotomy decreases the frequency of perineal sutures and that active management of the third stage of labor decreases hemorrhages. However, we will measure the effectiveness of their use in the context of our study.

2.4.2. Other secondary outcome

Provider's readiness to change with respect to episiotomies and management of third stage of labor.

3. Study Population and Procedures

3.1. Study Site and Populations

We will recruit hospitals in two countries because recruiting 24 hospitals in Uruguay alone is not feasible. In Argentina, we will recruit hospitals in the province of Buenos Aires and the city of Rosario. In Uruguay, we will recruit hospitals in the Department of Montevideo. Buenos Aires and Rosario are geographically close to the coordinating center in Montevideo. Even though intervention and control hospitals will be in the same cities, they do not share personnel and are independent entities.

3.2. Inclusion and Exclusion Criteria

3.2.1. Inclusion criteria for hospitals

Hospitals will be invited to participate in the study if they fulfill the following criteria:

- have an Institutional Review Board (IRB), or existing committee which could serve as such, or have an agreement with an IRB which reviews the research protocols implemented in the hospital;
- have at least 500 vaginal deliveries per year;
- do not have a explicit policy for selective episiotomy and for active management of third stage of labor; and
- consent to participate in the study.

Those preselected hospitals will perform a baseline data collection (see section 5.2). . According to the results of the analysis of the baseline data collection, hospitals will be excluded if the episiotomy rate is low or the rate of active management is high, according to the following cut-off points:

- Episiotomy rate in primiparous women with spontaneous vaginal deliveries below 70 %[1]
- Rate of active management of third stage of labor over 15% [2]

Because these hospitals do not have a policy for selective episiotomy or active management, it is expected that none of them will be excluded by this criteria. The sample size of the study was increased to allow for exclusions (see section 10.3).

1 This figure was selected based on a survey in 38 hospitals in Argentina. This study showed that the episiotomy rate was above 70% in 90% of the hospitals in the survey (Althabe et al., 2002).

2 A survey in 23 hospitals in Argentina and Uruguay showed an average rate for active management of the third stage of labor of 5%.

We interviewed the Head of the Obstetrical Department from 23 potentially eligible hospitals during the month of June 2000. Twenty-one confirmed that they were performing episiotomy routinely among primiparae, and 21 reported that expectant management during third stage of labor was the standard form of care (expectant management is defined as "a hands-free policy" during third stage of labor until the placenta is expelled: no use of uterotonics or special maneuvers).

3.3. Sampling, Recruitment, and Screening Procedures

CLAP coordination team will be responsible for the hospital selection. The hospitals' fulfillment of selection criteria will be obtained through a survey to the Heads of the Obstetrical Departments.

Besides the selection criteria, the coordination unit will invite the hospitals to participate according to

- their participation in previous trials coordinated by CLAP;
- their participation in other trials or research activities; and
- their location.

In Appendix 1, we show the characteristics of each preselected hospital regarding the structure of the professional staff, number of deliveries, and clinical guidelines policy.

3.4. Randomization Procedures

Preselected hospitals will perform a baseline data collection. According to the results of the analysis of the baseline data collection, hospitals will be excluded from the study if the episiotomy rate in primiparous women is below 70% or the rate of active management is higher than 15% (see section 3.2). Those hospitals fulfilling the inclusion criteria will be randomized to either the intervention or the control group.

This study has a maximum of only 24 hospitals to allocate to the control or intervention group, and random allocation may not provide adequate balance in the groups (Treasure and MacRae, 1998). In addition, stratified allocation may not be feasible due to there being too few numbers to stratify by all important variables (Treasure and MacRae, 1999).

Minimization has the particular advantage that it can make small groups of units closely similar with respect to several unit characteristics (Altman et al., 2001). A randomization lists is not set up in advance. The first unit is truly randomized, but in each subsequent unit the treatment allocation is identified which would minimize the imbalance between groups (Pocock, 1983). In this trial all units (hospitals) enters the study at the same time, and all prognostic variable are known in advance. In this situation a computer algorithm can choose by random one allocation sequence among a set of sequences that minimizes the imbalance between groups. Such algorithm will be used to allocate hospitals in this study.

Minimization offers an acceptable alternative to randomization, and some have argued that it is superior.(Treasure and MacRae, 1998). Trials that use minimization are considered methodologically equivalent to randomized trials according to the Consort

Statement (Moher et al., 2001), endorsed by the BMJ, JAMA, Annals of Internal Medicine and The Lancet, among others.

There are four hospital characteristics that were selected as important prognostic variables. These are the variables that will be included in the minimization algorithm to assure balance between groups.

1. Teaching hospital with residents (Yes-No).
2. Country (Argentina-Uruguay).
3. Hospital size (less than 2000 – 2000 or more deliveries per year).
4. Region (Montevideo, Salto/Paisandu, Rosario, Buenos Aires).

The minimization algorithm will minimize the imbalance between groups, assigning more priority to variables 1 and 2. table 2 shows the values for the selected variables for all 24 pre-selected hospitals, and table 3 shows an example of one set of results of the minimization algorithm on these hospitals.

After the baseline data collection period the dataset will be analyzed by RTI. RTI will then apply the inclusion criteria to assess the eligibility of preselected hospital according to the baseline rate of episiotomy and active management. The statistician at CLAP will elaborate a computer program implementing the minimization algorithm. The source code of the algorithm will be made available in advance to RTI and UNC-CH for audit and testing. This computer program will be used by the statistician at RTI to allocate eligible hospitals to either intervention or control without participation of others. The assignment will then be communicated to CLAP. Thus, there will be a clear separation between the generator of the intervention assignment and the CLAP study coordination (Donner et al., 1998).

Table 2. Hospitals characteristics to be included in the minimization algorithm.

Hospital	**Residents** **(1) Yes,** **(2) No**		**Country** **(1) Argentina,** **(2) Uruguay**		**Size** **(1) less than 2000,** **(2) 2000 or more**		**Region** **(1) Montevideo,** **(2)Salto/Paisandu,** **(3) Rosario,** **(4) Bs. Aires**	
San Roque	Yes	1	Argentina	1	1500	1	Bs. Aires	4
M.V.de Martínez	Yes	1	Argentina	1	3400	2	Bs. Aires	4
Héroes de Malvinas	No	2	Argentina	1	3000	2	Bs. Aires	4
Materno Infantil	Yes	1	Argentina	1	2800	2	Bs. Aires	4
Bocalandro	No	2	Argentina	1	2200	2	Bs. Aires	4
Hosp. De Clínicas	Yes	1	Uruguay	2	1000	1	Mvdeo	1
Germani	No	2	Argentina	1	2500	2	Bs. Aires	4
Roque Saenz Peña	Yes	1	Argentina	1	1660	1	Rosario	3
Paroissien	Yes	1	Argentina	1	2800	2	Bs. Aires	4
Alejandro Korn	No	2	Argentina	1	1300	1	Bs. Aires	4
Durand	Yes	1	Argentina	1	2000	2	Bs. Aires	4
Ramon Carrillo	No	2	Argentina	1	1250	1	Bs. Aires	4
Hospital Centenario	Yes	1	Argentina	1	1300	1	Rosario	3
Equiza	No	2	Argentina	1	2800	2	Bs. Aires	4
Manuel Belgrano	Yes	1	Argentina	1	1200	1	Bs. Aires	4
San Martín	Yes	1	Argentina	1	3000	2	Bs. Aires	4
Hosp. Militar	Yes	1	Uruguay	2	1800	1	Mvdeo	1
Hospital de Paysandú	Yes	1	Uruguay	2	2100	2	Paysandú	2

Eva Perón	Yes	1	Argentina	1	1700	1	Rosario	3
Narciso López	Yes	1	Argentina	1	1750	1	Bs. Aires	4
Hospital Provincial	Yes	1	Argentina	1	1400	1	Rosario	3
Hospital de Salto	No	2	Uruguay	2	1000	1	Salto	2
Santa Rosa	Yes	1	Argentina	1	3000	2	Bs. Aires	4
Virgen del Carmen	Yes	1	Argentina	1	1300	1	Bs. Aires	4

Table 3. Example of one possible set of results of the minimization algorithm.

Guidelines Trial

	Control	Intervention
Residents:		
Residents	9	8
No Residents	3	4
Country:		
Argentina	10	10
Uruguay	2	2
Hospital Size:		
Less than 2000	7	6
2000 or more	5	6
Region:		
Montevideo	1	1
Salto/Paisandu	1	1
Rosario	2	2
Bs. Aires	8	8
Totals :	12	12
Grand Total :	24	

3.5. Informed Consent

All control and intervention hospitals have to agree in advance to participate in the study. Hospital responsible authority (director or equivalent) will provide written consent to participation before randomization (Appendix 5). Hospitals will be informed of the assignment to control or treatment group following randomization. Individual health providers in the intervention hospitals will receive a fact sheet describing the objectives of the study, including the name and phone number of the country coordinator (Appendix 5). Birth attendants in the intervention hospitals will receive a fact sheet (Appendix 5) that provides them with information as to the format, length, and purpose of the training intervention; any benefits or risks they might incur as participants; their right to decline to participate without retribution; who to contact in case they have questions or concerns; and the fact that they will be informed of the results of the study. Birth attendants selected as opinion leaders in the intervention hospitals will provide written consent to accept that role in the implementation of the intervention (Appendix 5).

3.6. Management and Retention of Study Populations

The study subjects will be the health professionals working in participating hospitals, but the main outcomes will be measured among women having a delivery. However, there will be no follow up with the women, thus no special activities are planned with them.

We will monitor the activities of participating health professionals in relation with the compliance of the intervention, with the aim of (1) measuring the activities that will be considered as process outcome and (2) detecting protocol violations and make efforts to correct them (see section 4.6, Protocol Violations)

3.7. Reimbursements

No reimbursements will be provided to personnel of participating hospitals or women involved in formative research.

4. Study Intervention

4.1. Formative Research

To ensure that materials and interventions are effective, culturally appropriate, and readily integrated into routine care, we will conduct a descriptive qualitative research study that will have two stages designated to answer two specific objectives.

The aim of the first stage is to obtain and analyze information to refine the intervention strategy and all intervention materials. This information will allow us to (1) refine the design of the intervention, selecting the most culturally appropriate and acceptable components and materials' designed for health professionals and women and (2) better integrate the intervention into the hospitals' routine (i.e., identification process of hospital opinion leaders, scheduling in-service training and follow-up meetings). We will conduct in-depth interviews with upper level physician administrators and focus groups with second level physicians, midwives, and pregnant women. Also, additional focus groups, in the pilot hospital that has passed through an effective process of behavior change regarding selective episiotomy and active management, will be organized in order to explore factors associated with success.

The aim of the second stage is to assess the intervention materials' appropriateness. For this purpose, we will have personal communication with second level physicians and midwives who participate in the focus groups of the first stage. If, as a result of the research with women on the first stage, a communication module to women would be recommended as a component of the intervention, we will assess the women's opinions regarding the appropriateness of the materials through focus groups.

We have identified, within hospitals, two subgroups of physicians who set policies and procedures for pregnant women's care: upper level hospital administrators (responsible for the clinical an administrative management of the departments) and second level physicians (responsible for the individual provision of clinical care to users and coordinators of the daily clinical activities). We expect that these subgroups of physicians can give us valuable information for the design of our strategy because they have different roles in the clinical care process and could have different views and opinions about the process of implementing new forms of care into routine care. Also, we will include midwives´ perspective as a very important person in the role of delivery attendance, because in some hospitals they attend a large proportion of deliveries.

We will include the pregnant women's perspective since they are the direct beneficiaries of the intervention and because we are interested in the development of recommendations on women's involvement in the clinical decision-making process.

The focus group includes 8 to 10 participants. All focus group participants will be asked to provide informed consent. The informed consent form will be read aloud to the group to ensure that any patient with reading difficulties understands and can knowledgeably respond to the form. In addition to the facilitator, two recorders will also attend each group. One will serve as the note taker of the participants' comments; the other will record any unspoken language and group dynamics. Focus groups will be taped and transcribed. Participants to the

focus groups with pregnant women will be given small presents (i.e., diapers) in acknowledgment for their participation.

The researcher will carry out the in-depth interviews with upper level administrators. Each interview will be audio-taped for subsequent transcription by the data entry clerk. The interviewer will follow a semi-structured questionnaire. All interviewees will be asked to provide informed consent. We will begin with a minimum number of focus groups and in-depth interviews and continue with others if needed until the saturation criteria is fulfilled.

A four-stage strategy will be used to analyze data from the practice innovation and intervention materials focus groups. A computer program, Atlas-TI, will be used to analyze focus group and interview transcript texts (Barry, 1998). This program allows data analysts to code sections of text in more than one way and to compile selected portions that meet search criteria without destroying the integrity of the original transcripts.

Social Scientists at the University of North Carolina at Chapel Hill (UNC-CH) will work closely with CLAP's social scientist at Montevideo during the recruitment process. They will create the focus group and interview protocols, facilitate the focus group sessions, and analyze the qualitative data.

The detailed formative protocol is included in Appendix 3. The informed consent forms for the formative research are included in Appendix 5.

4.2. Creation of an interactive WWW portal

An interdisciplinary team from UNC-CH's Communication for Health Applications and Interventions (CHAI) Core, RTI, and CLAP will design, develop, and maintain a World Wide Web (WWW) portal that will serve as a user-friendly, Spanish language clearinghouse for information about evidence-based practice. This portal will afford practitioners with direct linkages to each other and to the CLAP study coordinators and principal investigators through the use of e-mail, online chat rooms, and discussion forum services. A health professional at CLAP will act as a local administrator of the portal once it is developed. The portal will be for the exclusive use of the professional staff at the intervention hospitals. In order to avoid the use of the portal by professional staff in the control hospitals that could lead to contamination, a password access system will be installed until the end of the intervention.

4.3. Intervention Description

4.3.1. General description

Opinion leaders in the 12 intervention hospitals will be identified by their peers through a specific questionnaire (Appendix 6) and trained by the Country Coordinator and assistant instructors to develop evidence-based guidelines. They will then use a multifaceted approach to disseminate, implement, and maintain the guidelines. The approach will include seminars, academic detailing, reminders, and feedback on utilization rates. The refinement of the intervention will be done considering the information obtained in the formative research. Therefore, the components described below could be modified after that stage.

4.3.2. Components of the intervention

4.3.2.1. Pre-randomization components

4.3.2.1.1. Selection of hospitals

A total of 24 hospitals from Argentina and Uruguay will be selected. The 4 selected hospitals in Uruguay are located in Montevideo (2), 1 in the city of Paysandú, and 1 in the city of Salto. The 20 selected hospitals in Argentina are located in the Province of Buenos Aires (15), in the city of Buenos Aires (1), and in the city of Rosario (4).

Hospitals were selected if they fulfill the following criteria:

- have an Institutional Review Board (IRB), or existing committee which could serve as such, or have an agreement with an IRB which reviews the research protocols implemented in the hospital;
- have at least 500 vaginal deliveries per year;
- do not have a explicit policy for selective episiotomy and for active management of third stage of labor; and
- consent to participate in the study.

4.3.2.1.2. Delivering of information to hospitals

Hospitals may differ by the level of contact that their staff have with evidence-based literature, although CLAP is providing such information to Latin American obstetric departments on routine basis. In order to insure that hospitals received the same level of previous information from CLAP, heads of the obstetric departments will receive copies of CLAP's newsletters and publications from the past 2 years, and a copy of the WHO Reproductive Health Library (RHL). The presentation of the study to the authorities of preselected hospitals, and the delivering of the bulletins and the RHL will be done in a general presentation meeting to hospital authorities, and in meetings at each participating hospital during the preparation phase.

4.3.2.2. Post-randomization components

4.3.2.2.1. Presentation of the intervention at intervention hospital

The intervention will be presented in a seminar to all health professionals (physicians, nurses and midwives) in the hospital. The objectives of this

component are to explain to birth attendants the organization of the intervention and birth attendants' roles and motivate birth attendant's behavior change. The contents of the seminar will be

- the problem: how busy physicians can be updated;
- a general description of the intervention; and
- the selection of the opinion leaders' team.

The seminar will be 60 minutes long and the day and time will be planned in advance in order to allow most of the staff to participate.

Attendance of hospital professional staff to the meeting will be documented by the data supervisors.

4.3.2.2.2. Selection of opinion leaders.

Each intervention hospital will select a team of opinion leaders that will work together and support each other during the workshops and upon their return to the hospitals.

The selection process will be done by peer nomination within all the professional staff of the maternity hospital or department of obstetrics. A sociometric questionnaire will be used as the instrument to identify the opinion leaders among the professional staff (Appendix 6). The questionnaire will consist of three statements describing the following sets of personal characteristics that have been shown to be associated with opinion leaders (Hiss et al., 1978):

- *Knowledge:* to be current and up to date, and demonstrate a high level of expertise.
- *Communication:* professionals who enjoy and are willing to share knowledge, that never seem to busy to be helpful, and that offer clear and practical information.
- *Humanism:* caring physicians, never talking down to their colleagues.

The appropriateness of the questionnaire will be assessed in the formative research.

Each professional will be asked to suggest the names of the professionals within their hospital or department that fulfill each category. Thus it is possible that different names are nominated below each statement. The professional/s nominated in the **3 categories** will be selected as opinion leaders. If no professional was nominated in the 3 categories, then those nominated in 2 categories will be selected. Finally, if no professional was nominated in 2 categories, then those nominated in 1 category will be selected. We do not expect a hospital were no professionals are nominated in at least one category.

The head of the department will be invited to designate one professional not included in the nominated team, if they like to.

The selected professionals will be offered to be part of the team of opinion leaders (referents) irrespective of the number selected at each hospital.

Data supervisors will administer and coordinate the selection process that will be held during the presentation meeting. Non attendants will be contacted later.

This process is provisional and the final selection process will be adapted according to the results of the formative research.

4.3.2.2.3. Guideline Development

The opinion leaders' teams will participate in regional 5-day workshopsseries. The workshops will be given in 5 consecutive days, for 8 hours per day, in a previously selected site outside the hospitals prepared with computers with internet connections. The practical module of clinical application will be carried out with dummy models. The workshops will be conducted by the country coordinator and trainers who will act as tutors. Each one will guide one group with no more than 10 participants. Both will have diverse experience in conducting these workshops in Latin American countries. Two workshops will be carried out in Buenos Aires and one in Montevideo. Opinion leaders' teams from Rosario will travel to Buenos Aires to participate in the workshops.

The objective for the workshop is that participants will be able to answer two questions:

1) Should episiotomy be performed routinely or selectively to prevent perineal damage?

2) What is the best way to manage the third stage of labor in order to prevent post partum hemorrhage?

The main task will be to develop simple clinical guidelines formulated as clinical recommendations and to practice how to deliver the recommended interventions.

The objective of the practical module is to apply the new abilities proposed in the guidelines, first in dummy models and then in patients. This methodology could accelerate the learning process and also could allow humanized teaching.

Topics to be considered at the workshop:

- How to formulate feasible clinical questions based on a clinical situation.
- Bibliographic search of published literature to answer the clinical question.
- Critical appraisal of the literature.
- The steps to evaluate a therapy or prevention article (randomized clinical trial).
- The steps to evaluate a systematic review of randomized clinical trials.
- Methodology for the preparation of clinical guidelines based on the evidence.
- Practical activity: How to assist a delivery without an episiotomy and the active management of the third stage of labor.

The guidelines will be built and adopted by consensus, based on the analyzed evidence. The consensus process will be greatly facilitated by the homogeneity of the results of published trials on episiotomy and active management of third stage of labor. Guidelines will include recommendations on women's involvement in the clinical decision process.

The workshop will have the following evaluations:

- Participants' knowledge on critical appraisal skills: a simple test based in seven multiple choice questions will be administered on the first day and on the last day.
- Opinions about active management and selective episiotomy and satisfaction with the developed guidelines.
- Skills developed in practical sessions.
- Satisfaction of the participants with the workshop.

These evaluations will be part of the process outcome measurement. Participants will be given certificates from CLAP.

4.3.2.2.4. Dissemination:

Each opinion leader's team and assistants will return to their hospital and lead the dissemination effort.

The objectives of this component are to

- select a group of potential early adopters (volunteers) who are willing to participate in the implementation of the guidelines;
- identify discrepancies between the guideline recommendations and practice in their hospital;
- identify barriers to changing current practice;
- identify strategies for overcoming these barriers; and
- develop an implementation time table.
- for that purpose opinion leaders will:
- present the guidelines in a seminar to all health professionals in obstetric practice;
- present and introduce the use of the WWW portal to all health professionals; and
- do personal visits to each birth attendant who could not attend the seminar or want more explanations or more details about the guidelines, the process to develop them, and the use of the portal (academic detailing).

Compliance with this component will be documented measuring the attendance of the professional staff to the seminar, and the number of personal visits.

4.3.2.2.5. Web Portal

During this period, a personal computer will be installed at each hospital. This computer will already have the Cochrane Library, the Reproductive Health Library (RHL), and an internet connection installed.

A specially designed, interactive WWW portal will be the default home to Internet. It will serve as a user-friendly, Spanish language clearinghouse for information about evidence-based practice. This portal will afford practitioners with direct linkages to each other and to CLAP study coordinators and principal investigators through the use of e-mail, online chat rooms, and discussion forum services. It will provide a number of specific services to help motivate practitioners to pursue evidence-based practices, and provide them with the knowledge and skills they need to implement evidence-based guidelines. The portal will feature links to the latest Spanish-language resources on evidence-based practice and to the hospital-specific guidelines for episiotomies and management of the third stage of labor developed by the local opinion leaders. The portal will also afford practitioners with linkages to (1) experts on evidence-based practice, (2) their local opinion leaders, and (3) each other, via e-mail, on-line chat, and discussion forum services. A health professional at CLAP will act as a local administrator of the portal once it is developed. The portal will be for the exclusive use of the professional staff at the intervention hospitals. In order to avoid the use of the portal by professional staff in the control hospitals that could lead to contamination, a password access system will be installed until the end of the intervention. One of the professionals selected for the workshops should be able to help with the use of all electronic resources. Detailed protocol of the portal development is included in Appendix 2.

4.3.2.2.6. Implementation

This stage has an estimated duration of 3 months and will include the following activities:

- Placing Reminders: there will be short messages that remind birth attendants to consider two interventions:
  - Active management reminders: to be placed at least in the partograph and as posters in the delivery ward.
  - Selective episiotomy reminders: to be placed at least in the surgical package for assisting delivery and in the partograph.
- Recommendation to prepare ready-to-use packages for active management of third stage: CLAP study coordinator will provide instructions on how to prepare the packages.
- Monthly monitoring of the rates of episiotomies and the use of oxytocin at the hospital level, and feedback to birth attendants, through the use of the Perinatal Information System (PIS). The opinion leaders will have to produce monthly reports and ensure that each staff member receives one copy of it. CLAP study

coordination will not be involved in the production of the reports, and no copies will be sent to CLAP.

These three interventions are compulsory for the component compliance to be considered positive and will be monitored and documented. Opinion leaders can implement these activities more intensively (eg. posting more reminders, producing more reports), or implement other strategies to overcome barriers identified in the dissemination section: For example, strategies may include providing explanation and assistance to birth attendants on how to assist a delivery without performing an episiotomy.

CLAP country study coordinators and hospital coordinators in control and intervention hospitals will monitor the availability or oxytocin for active managements. In case of shortage of supply the study will provide the drugs.

4.3.2.2.7. Maintenance

It is estimated that this stage will last 6 months. The compulsory activities will be the use of reminders and the monthly monitoring reports. The difference between the two stages is that during maintenance, CLAP study coordination will not provide additional support activities. The WWW portal will be a major tool in this period, through the provision of services to help motivate and continuously update practitioners to pursue evidence-based practices and provide them with the knowledge and skills they need to implement-evidence based guidelines.

4.4. Delivery of the Intervention

The country coordinator will contact the intervention hospitals to communicate the random assignment allocation and to arrange the logistics for the initiation of the intervention.

Two workshops will be conducted in Buenos Aires and one in Montevideo. Opinion leaders' teams from Rosario will go to Buenos Aires to participate in the workshops.

The dissemination, implementation, and maintenance components will be delivered in each hospital.

4.5. Control Group

The control group will receive no intervention after randomization but will be asked to continue with their standard in-service training activities and the use of their standard sources of information. We will give birth attendants the guideline development component, the computer and the electronic resources *following* the completion of the intervention stage. Birth attendants will be allowed to use data from the routine data collection done through PIS.

4.6. Protocol Violations

4.6.1. Pre-randomization

- Inclusion criteria violation: to randomize hospitals that have episiotomy rates < 70% in vaginal deliveries of primiparous women, or active management of third stage of labor > 15%

4.6.2. Post-randomization

Compliance with the intervention (intervention hospitals)

- Pre-intervention delivering of information to hospitals: not giving the RHL and CLAP's Bulletins to all participating hospital authorities.
- Presentation of the intervention at the hospitals: more than 25% of staff not attending the seminar.
- Selection of opinion leaders: using other methods to select the opinion leaders' teams; each existing profession at the hospital not being represented in the team.
- Workshops: no attendance of more than 30% of opinion leaders' teams more than 30% of the workshop time.
- Dissemination and implementation: not presenting the guidelines and Web portal to all staff members.
- Implementation:
  - not producing or delivering the monthly reports
  - not placing reminders in partograph or clinical record, and labor wards (active management), and in partograph or clinical record, and surgical package for assisting delivery (selective episiotomy).

Contamination with intervention materials (control hospitals)

- The explicit use of materials specially designed for, or used in, the intervention in in-service training activities.

The violations will be detected through the continuous monitoring system that will be established at the Data Unit at CLAP. If a protocol violation is detected at the intervention hospitals, coordinators in Argentina and Uruguay will be in charge of contacting the opinion leaders' team in order to assess the problems to comply and establish corrective and preventive measures. In control hospitals, assessment of the in-service training activities will be done through the coordinators and data supervisors on a quarterly basis.

This list of protocol violations is provisional. The final list will be developed after the refinement of the intervention, following the formative research.

4.7.Adverse Events

Adverse events in health providers (study subjects)

Although we do not expect adverse events in the study subjects, it might be possible that the active participation (or not participation) of the health providers in the intervention could originate conflicts among some of them, or with the hospital authorities, related to the implementation of the new guidelines in clinical care. It also might be possible that some women had conflicts with the birth attendants related to the use (or non-use) of the practices recommended in the new guidelines. These kinds of conflicts could be interpreted as adverse events if they led to

- loss of job positions or
- malpractice lawsuits.

CLAP study coordination will monitor the changes in the health providers' staff composition on a weekly basis. If any health provider resigned or was fired, a specific questionnaire will be completed considering the motives (from the hospital and the subject's point of view). Reports will be sent to the corresponding staff at the Data Center and National Institute of Child Health and Human Development (NICHD) within 7 days of identification. CLAP study coordination will ask the Head of the Obstetric Department in each hospital to report all malpractice lawsuits directed toward the department's health providers. The coordinators will also specifically address this issue with the Head of the Department on a quarterly basis. If any health provider received a malpractice lawsuit, resigned or was fired, a specific questionnaire will be completed considering the terms of the suit and the time period of the event that originated it. Reports will be sent to the corresponding staff at the Data Center and NICHD within 7 days of identification.

Adverse events in women and children

Although women and their offspring are not subjects in this study, they are the ultimate beneficiaries of the health practices promoted in the intervention. We do not expect adverse events associated with the behavioral intervention on health providers. However, we will continously monitor in-hospital maternal deaths and early neonatal deaths up to discharge from hospital. The routine data forms of the PIS include maternal and neonatal status at discharge (alive, death), and they will be monitored on daily basis through the data collectors during all the study period. To be able to assess women who are readmitted, the Head of the Department will be be instructed to report any maternal death occurring in the hospital, also on a daily basis.

In case of a maternal death, a specific case report form will be completed with the following information: date, time of onset; clinical history; medical management, including rationale; pertinent laboratory tests; relevant past medical history; autopsy report or expectation of an autopsy; location/study center; reporting physician; verification of notification to IRB, Data Safety and Monitoring Board (DSMB), and the Data Center (see appendix 3 for the form).

The death will be reported to the corresponding staff at the Data Center, NICHD, and IRB within 2 days of the occurrence.

To monitor neonatal deaths, monthly monitoring reports on the number of in-hospital early neonatal death (up to 7 days of life) and number of live births in the same period will be produced and sent to the DSMB.

5. Measurement Methods

5.1. Description of Questionnaires

5.1.1. Clinical data collection instruments

Although the hospital will be the unit of analysis, we will collect patient data in order to obtain high quality data. We will collect data on primary and secondary outcomes and on potential confounders or effect modifiers. We will also collect data for safety monitoring (neonatal morbidity and mortality and maternal mortality). For clinical data there are 4 data collection forms (see appendix 6). CLIN1 form will collect data at the time of delivery, and ALTA1 will collect data on events from delivery to postpartum discharge. CLIN1 and ALTA1 forms will be used at data collection periods I and III. CLIN2 and ALTA2 will be used in data collection period II and IV (see figure1 and section 5.2). The only difference between these two sets of forms is that CLIN1 and ALTA1 collect data on post-partum blood loss, while CLIN2 and ALTA2 do not.

All the hospitals in the project use a standard perinatal clinical history form (PIS form). This form registers the data of the obstetric history, prenatal care, labor, delivery, and neonatal outcomes. The additional information is recorded in other instruments and varies according to the hospital (i.e. laboratory results, ultrasound, etc.). This form was developed by CLAP in 1984 as a part of technical cooperation provided by the Centre to the countries in Latin America and the Caribbean. Some, but not all of the hospitals in the study enter the data in this document format using a computer program that was also developed by CLAP.

The forms for the data collection (CLIN1 and ALTA1) have 38 variables; only 11 of those variables are not in the perinatal clinical history of PIS. These variables are not registered in any other data collection instrument in the clinical record. These are variables with information that should be recorded immediately after delivery (active management of the third stage, retain placenta, second and third degree tears, etc.), and because deliveries occur 24 hours/7 days a week, the data must be collected by personnel that are always present in the delivery room, such as birth attendants or nurses. To obtain these additional data, CLAP will implement a modified version of the PIS clinical record containing the additional variables during the data collection periods. This approach will reduce to a minimum the extra activities associated with data collection that the birth attendant will need to perform during the study. The alternative to this option would be the introduction of a new paper data collection form, but as mentioned before, most of the information will be copied from the PIS form anyway.

5.1.2. Questionnaires to birth attendants

A self administered "Readiness Questionnaire" (RQ) (Appendix 6 for the form and Appendix 5 for the informed consent) was designed to assess physicians' and midwives' perceived current practices in managing the third stage of labor and episiotomy practices; their beliefs in and perceived barriers to conforming to the evidence-based guidelines; interventions they are receptive to (e.g., feedback, academic detailing); and their commitment to improvement (Main et al., 1995).

5.1.3. Process data

Data will also be collected to monitor the process of the intervention. A description of forms and methods for process measures can be found in section 5.6..

5.2. Schedule of Data Collection

Table 4 presents the components and the schedule for data collection in the project. There are three different sets of data to be collected, and the data collection system will be different for each one. These are

1. clinical outcomes,
2. readiness to change questionnaire to health providers, and
3. process measures.

Clinical outcomes and readiness to change questionnaire includes the primary and secondary outcomes of the project and will be measured in all participating hospitals (intervention and control harm). Process measures will be used to explore aspects of the intervention implementation, and they will be measured only in the intervention hospitals.

Clinical data will be collected in four periods, and each will be 1 year apart (Table 4):

- Period I. Baseline data collection: before randomization in the preparatory phase, for primary and secondary outcomes.
- Period II. Mid-intervention data collection: immediately before the implementation of the guidelines, for primary outcomes only.
- Period III. Main post-intervention data collection: immediately following the maintenance component of the intervention, for primary and secondary outcomes.
- Period IV. Second post-intervention data collection: 1 year after the main post-intervention data collection, for primary outcomes only.

Data from period I (baseline) and III will be used for the primary analyses, and include both primary and secondary outcomes. Secondary outcomes include nonroutine procedures to measure blood loss (see below). Data collection II will be used to study trends and will be limited to primary outcomes, which can be measured without interference with the clinical processes. Data collection IV will be used to measure the sustainability of the results after the end of the intervention and will also be limited to primary outcomes to avoid interference with the clinical processes.

Table 4. Schedule for data collection.

	Year							
	1	2	3	4	5			
Project Stage	**Preparatory Phase (Data Collection I - Baseline)**		**Intervention Phase (Data Collection II)**	**Manteinance Phase (Data Collection III and IV)**	**Analysis and wrinting-up**	**hospitals**	**Forms**	**Tools for Data Entry & validation**
Project clinical outcomes. **Development and testing** **Training and implementation in Hospitals** **Data collection - Primary Outcomes** **Primary outcomes + blood loos**		I	III	III	IV	24	**Clinical Data Form (CLIN1, ALTA1, CLIN2, ALTA2)**	**Data Management Systems in hospitals**
Readiness to change **Data Collection - Providers' opinion**		I		III		24	**Readiness to change questionnaire (READY1)**	**Paper forms (Data entry at CLAP)**
Process measures (only intervention group) **Data Collection**						12	**To be developed**	**Paper forms (Data entry at CLAP) - Web Portal**

5.3. Questionnaire Administration

5.3.1. Clinical data

Data will be carbon copy from the clinical record. See section 5.1

5.3.2. Questionnaires to birth attendants

Questionnaires will be administered to all birth attendants in the participating hospitals prior to randomization (immediately after Period I) and after the end of the intervention (immediately after Period III).

5.3.3. Process data

Process data will be collected during the 18 months of the intervention at the intervention hospitals. The data collector will keep a logbook including the date the feedback reports were distributed and the date, place, objectives, and number of participants in meetings where health providers discussed the guidelines. A form will be completed after each academic visit and will include the date, the length of the visit (minutes), the training of the person visited, and the material used during the visit. During the month following the end of the intervention, a questionnaire will be sent to the directors of the hospitals of the control group to estimate the diffusion activities that might have occurred. A description of forms and methods for process measures can be found in section 5.6..

5.4. Collection of Biological Samples

5.4.1. Measured total blood loss (ml)

Nurses, midwifes and physicians who are a part of the teams attending deliveries at participating hospitals will be trained in post-partum blood loss measurement. Nurses and midwifes will be the main persons responsible for the measurements. Both the country coordinators and the data collection supervisors will be in charge of training. A pilot study will be implemented at the pilot hospital in Montevideo (Pereira Rossell) to assess the acceptability of the measuring technique.

Measurement technique:

A plastic bag designed to collect blood (drape) will be used to collect post-partum blood loss. The drape is made of transparent plastic and will not be calibrated.

As soon as the baby is delivered, the drape is placed under the buttock. The blood is allowed to collect into the drape as long as the woman stays in the delivery bed or chair. The time of delivery and the time when the blood collection starts and finishes will be recorded. At the end of the blood collection period, the amount of blood loss will be measured by weighing the drape on a scale provided by the study and translating g to ml. The blood and collection drape will be properly disposed of once weighed and the amount of blood loss will be recorded in the CLIN1 form by the birth attendant or the nurse.

5.5. Primary and Secondary Outcome Measures

Outcome rate will be assessed at the end of the intervention period in all hospitals (data collection period III) (Table 4).

5.5.1. Primary outcomes

- Episiotomy rate:

  Number of episiotomies among single vaginal deliveries.

- Active management of third stage of labor:

  Number of women who received injections of 10 International Units of oxytocin during third stage of labor, among single vaginal deliveries.

5.5.2. Secondary outcomes

5.5.2.1. Clinical secondary outcomes

- Perineal sutures:

Number of women with at least one perineal suture among single vaginal deliveries.

- Postpartum hemorrhage >500ml:

  Number of women with measured total blood loss >500ml among single vaginal deliveries

5.5.2.2. Other secondary outcome

Provider's readiness to change with respect to episiotomies and management of third stage of labor.

5.6. Process Evaluation Measures

The objectives of the process evaluation are to

- allow early detection of implementation problems so that they can be corrected;
- detect implementation problems that could be causal, in case of no effect; and
- facilitate the replication of the intervention, in case of being effective.

We will consider process measures within three categories:

- Program inputs
- Implementation activities
- Stakeholders reactions

A provisional list of outcome measures is shown in the Table 5. This list could be modified after the refinement of the intervention.

Table 5. Process measures.

Process Outcome	Data needed	Intervention phase	Data collection method
Program Inputs			
Availability of information technologies resources for staff	Place, accessibility to computer by all staff	Implementation	Data Form 1 (Proc 1). One by hospital. Managed by data supervisors
Implementation Activities			
Attendance of presentation seminar	Name of attendants. List of hospital professional staff	Presentation	Special data form. One data form by hospital. Collected by data supervisors
Opinion leaders´ team composition	Nº of and category of professionals	Selection of opinion leaders´ team	Special data form. One data form by hospital. Collected by data supervisors
Attendance of workshops	Nº of attendants and composition, Nº and composition of team	Workshops	Special data collection form. Managed by data supervisors.
Attendance of dissemination in-hospital activities (seminar and personal visits)	Name of attendants. List of hospital professional staff	Dissemination	Special data form. One data form by hospital. Collected by data supervisors
Implementation activities below minimum (see 4.6)	Nº of monitoring reports (episiotomy rates and active management) Use of reminders Use of active management packages	Implementation	Outlook type software to register activities. Automatically/by hand by hospital coordinator
Web portal use	Web site visits E-mail consultations Participation in discussion forums	Implementation and maintenance	Automatic data collection through the software and website
Stakeholders reactions			
Knowledge acquired, attitudes to developed guidelines, opinion about selective episiotomy and active management, satisfaction with workshop	Knowledge of Evidence-Based Medicine (EBM), critical appraisal, opinion about guidelines, satisfaction with workshop (objectives accomplished, materials)	Workshops	Pre and post workshop test (knowledge) Specific questionnaires to evaluate attitudes to guidelines). Questionnaire to evaluate satisfaction. One per participant.

6. Training Study Personnel in Data Collection

The training will be done during the preparatory phase, among other activities. This phase will take approximately 18 months. The Data Manager will coordinate the training in data collection procedures. The pilot of the manual of operations for data collection and data collection forms will be done in one hospital in Montevideo, Uruguay, and one hospital in Buenos Aires, Argentina. Those hospitals will not be randomized, but will be similar to those that will be assigned to the intervention and control group.

6.1. Job Descriptions of Study Personnel

The data collection system will be centrally coordinated at CLAP by a statistician. The team at CLAP will include one programmer, one statistical assistant and two data clerks. The computer programmer at CLAP will develop the software for data collection and validation. The statistical assistant will carry out day to day data management activities (communication with data supervisor and data clerks at the hospitals, production of monitoring and validation reports, etc). For paper forms sent to CLAP, the two data clerks will perform two independent data entries.

Two data supervisors in Argentina and one data supervisor in Uruguay will implement and supervise the data collection at the country level throughout the study period. Data supervisors will visit hospitals usually on a weekly basis, although the frequency of visits may vary according to hospital performance and needs. They will be nurses or midwifes working part-time for the study. They will have expertise in clinical research and data management in collaborative trials.

There will be one in-hospital data collector in each hospital. In most cases, this personnel will be one hospital employee that will work part-time for the project. Usually an administrative that is responsible for data entry in the hospital. They will carry out data entry and validation at the hospital level.

6.2. Training of Recruiters

Not applicable.

6.3. Training of Biological Sample Collectors

Nurses or midwives in the labor ward of each hospital will be trained in how to measure total blood loss in vaginal deliveries. They will be trained to perform this measurement as a routine activity in all vaginal deliveries during the data collection periods. Data supervisors and Country coordinators will be in charge of the training activities and will provide hospitals with the standard measuring drapes.

6.4. Training of Process Evaluation Personnel

Intervention hospitals data clerk will be trained to enter data in PIS, although the people usually responsible for PIS data entry will be the intended personnel for this task. Also the data clerk will keep a logbook including the date the feedback reports were distributed and the date, place, objectives, and number of participants in meetings where health providers discussed the guidelines.

6.5. Training Materials

The manual of operations for data collection and the data collection forms will be the main training material and will be developed and tested during the preparatory phase.

6.6. Certification of Recruiters, Interviewers, Biological Sample Collectors, Laboratory and Process Evaluation Personnel

Data supervisors in Uruguay and Argentina will be trained and certified at CLAP headquarters. Data collection and data management at the hospital level will be performed by hospital personnel that will be hired part-time by the study. These personnel will be trained by the data supervisors, and they will have to pass a standardized certification procedure before the beginning of the data collection. The data supervisors will apply the certification procedures. The certification procedure will be developed at CLAP in collaboration with the UNC-CH biostatistician. In order to be certified, these personnel will need to demonstrate a good working knowledge of the data management system (DMS) developed for the study, including procedures to assure data quality and patients' confidentiality. These personnel will also be trained in ethical issues in research with human subjects and will go through the online web training provided by the Office for Human Research Protection (OHRP), U.S. Department of Health and Human Service.

6.7. Maintenance of Training and Certification

During the study, the DMS will produce weekly reports to monitor data quality, by hospital, in order to identify problems in particular sites. If a hospital does not fulfill the quality standards the data supervisor will increase the frequency of the visits to this site and eventually retrain the data collector. All data collectors and data supervisors will have to pass a recertification exam each year. The hospital data manager will be assessed by the data supervisors. Data supervisors will be assessed at CLAP headquarters.

7. Training Study Personnel in Intervention Delivery

As for data collection procedures, the training in intervention delivery will be done during the preparatory phase. This phase will take approximately 18 months. CLAP study coordinator will coordinate this training. The pilot of the manual for the intervention will be done in the same pilot hospitals in Argentina and Uruguay. Those hospitals will not be randomized but will be similar to those that will be assigned to the intervention or control group.

7.1. Job Descriptions of Study Personnel

Research Associates

They will act as country coordinators in each study site (Province of Buenos Aires, Rosario and Montevideo). They will be in charge of the daily management of the trial in each site, will be the main contact person of the opinion leader's team with CLAP study coordination, and will actively participate in the workshops as tutors. The amount of daily work is estimated to be, on average, a 50% dedication to coordinate 4 hospitals in Rosario or Montevideo and 75% to coordinate 10 hospitals in Buenos Aires Province. Qualifications for these positions include being obstetricians, being respected by their peers, have training in Epidemiology or evidence-based medicine, and have experience working as tutors in evidence-based medicine or guideline development workshops.

Trainers

They will participate as tutors in the guideline development workshops. Each workshop will have at least two tutors and the Buenos Aires workshop will need three tutors (five hospitals, four participants in each one). The qualifications for these positions are to be health professionals (MD, epidemiologists) with previous experience in conducting evidence-based medicine or guideline development workshops.

7.2. Training of Intervention Staff

Study coordinators and trainers will be in charge of the implementation of the intervention. They are actively participating in the design of the intervention and are part of the Coordination Unit at CLAP. The intervention staff will be trained while piloting the intervention in the pilot hospitals.

7.3. Training Material

The materials for the training and guidelines development workshops will be produced and tested by CLAP in this phase. The guideline development component of the workshops will follow a model developed by CLAP in 1998, adapted from the McMaster's Evidence-based Clinical Practice Workshops (Neufield et al., 1989; Oxman et al., 1993). This workshop is currently one of the teaching activities of CLAP. Our innovative addition to this workshop will be to include the WWW portal as a major tool to link with Medline and evidence-based

sources. The materials to train the participants in the use of the portal will be developed and tested.

The manual of procedures for the dissemination, implementation, and maintenance components will be developed by the study coordination at CLAP. Experts in the field of changing professional behavior field from the UNC-CH, participating in the project will supervise the training of the coordinators with respect to the last three mentioned components.

7.4. Certification

Not applicable. The study personnel in charge of the implementation of the intervention will also be actively participating in the design of the intervention.

Birth attendants in participating hospitals are study subjects, and they will receive and not deliver the intervention. No certification procedure will apply to them.

7.5. Maintenance of Training

It is not necessary. The intervention will be given only once to the intervention hospitals.

8. Training in Ethical Issues

All country coordinators and data supervisors will be trained taking the web-based ethical course provided by the OHRP. In-hospital data collectors will be trained with the same course, for those skilled in the English language. For those personnel unskilled in the English language, and in case a Spanish version is not available for that moment, the training will be given by the country data supervisors, following the indications of OHRP.

9. Data Collection and Management

9.1. Overview

As described in section 5.2, Table 4 presents the components and the schedule for data collection in the project. There are three different sets of data to be collected, and the data collection system will be different for each one. These are

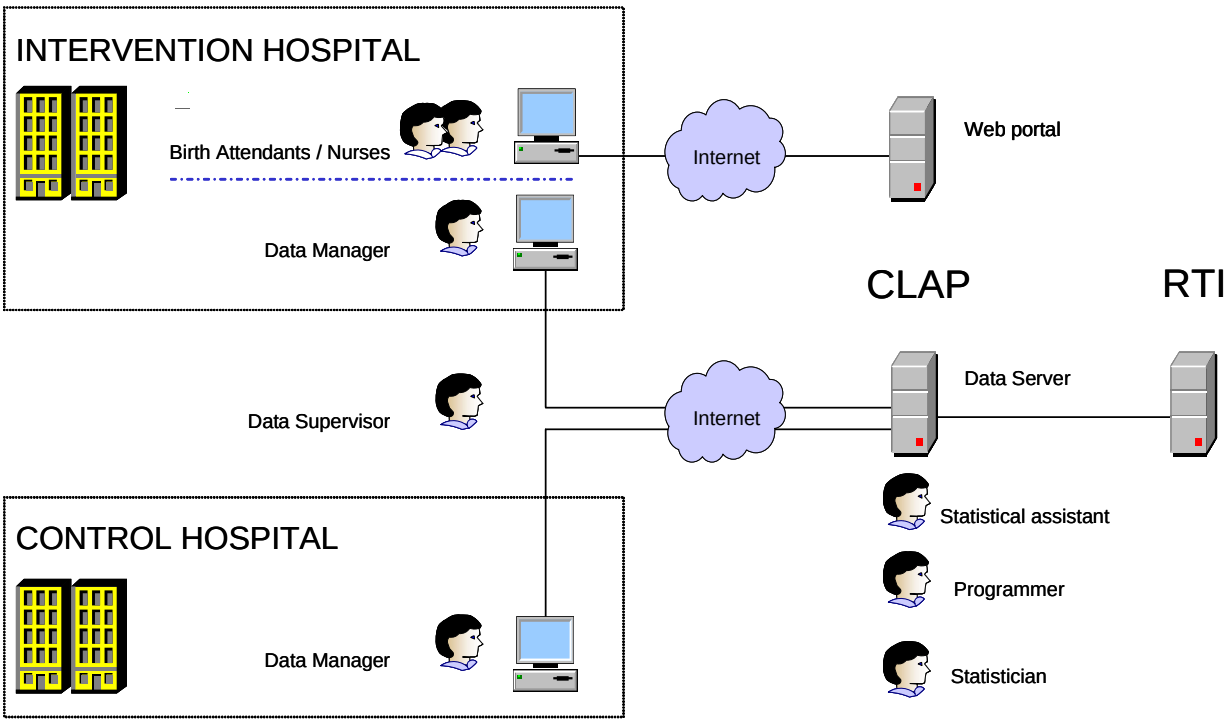
1. clinical outcomes,
2. readiness to change questionnaire to health providers, and
3. process measures.

Clinical outcomes and readiness to change questionnaire includes the primary and secondary outcomes of the project and will be measured in all participating hospitals (intervention and control harm). Process measures will be used to explore aspects of the intervention implementation, and they will be measured only in the intervention hospitals.

Figure 2 presents a summary of all the staff that will be involved in data collection. All hospitals will receive one computer that will be used only for data management and operated by the data manager. Intervention hospitals will receive a second computer, but this equipment will be used by birth attendants and will have no role in data collection for primary and secondary outcomes. It will be used, however, to gather data on certain process measure, only in intervention hospitals.

The data collection system will be centrally coordinated at CLAP by a statistician. The team at CLAP will include one programmer, one statistical assistant, and two data clerks. The computer programmer at CLAP will develop the software for data collection and validation. The statistical assistant will carry out day-to-day data management activities (communication with data supervisor and data clerks at the hospitals, production of monitoring and validation reports, etc). For paper forms sent to CLAP, the two data clerks will perform two independent data entries. Two data supervisors in Argentina and one data supervisor in Uruguay will implement and supervise the data collection at the country level during the whole study period. Data supervisors will visit hospitals usually on a weekly basis, although the frequency of visits may vary according to hospital performance and needs. One data manager will be hired in each hospital. In most cases, this personnel will be one hospital employee that will work part-time for the project.

Figure 2. Staff involved in data collection.



Project clinical outcomes include the primary and secondary clinical outcomes for the study (e.g., episiotomy rate and active management during the third stage of labor). The instruments for data collection are the clinical data collection forms (CLIN1, ALTA1, CLIN2 and ALTA2) (Appendix 6). The only difference between the two forms is that CLIN2 contains blood loss in milliliters (see Appendix 6 for data collection forms.)

Bias minimization: Data on outcomes will be collected for all the hospitals in the study (24 hospitals). The data collection system for outcomes will be independent from the implementation of the intervention. Given the nature of the intervention, we cannot blind the randomization, and data collectors will know if they belong to an intervention/control hospital. Furthermore, intervention hospitals will receive a computer to implement the intervention, which will be used, among other things, to monitor clinical data (i.e., episiotomy rate and active management of the third stage of labor). As a consequence, it is expected that the intervention will improve the capacity of intervention hospitals to collect and review clinical data and bias might be introduced in outcome assessment. To minimize this problem, the data collection system will be isolated from the intervention instruments as much as possible. In practical terms, this means that data collectors at the hospital level, data supervisors and computer hardware for data collection will have no role associated with intervention activities.

Data sources and data collection forms: Figure 3 presents a summary of the proposed system for data collection. All hospitals in the project currently use a standard clinical record (PIS form) developed by CLAP. This is a paper form that registers data on obstetric history, antenatal care, labor, delivery, and neonatal outcomes. Additional information is recorded in

other instruments depending on the hospital (i.e. laboratory results, ultrasound results, etc.). Because PIS is the clinical record, the form is completed for all women, and data is recorded during hospital admission, labor, delivery, and discharge from hospital. This form was developed by CLAP in 1984 as part of technical cooperation provided by the center to countries in Latin America and the Caribbean. Some, but not all, of the hospitals in the study enter the data in the PIS paper form in computer format using a program that was developed by CLAP.

The forms for the data collection (CLIN1 and ALTA1) have 38 variables; only 11 of those variables are not in the perinatal clinical history of PIS. These variables are not registered in any other data collection instrument in the clinical record. These are variables with information that should be recorded immediately after delivery (active management of the third stage, retain placenta, second and third degree tears, etc.), and because deliveries occur 24 hours/7 days a week, the data must be collected by personnel that are always present in the delivery room, such as birth attendants or nurses. To obtain these additional data, CLAP will implement a modified version of the PIS clinical record containing the additional variables during the data collection periods. This approach will reduce to a minimum the extra activities associated with data collection that the birth attendant will need to perform during the study. The alternative to this option would be the introduction of a new paper data collection form, but as mentioned before, most of the information will be copied from the PIS form anyway.

One problem in the vast majority of hospitals is that information on neonatal outcomes is usually missing, in particular for newborns admitted to intensive care (NICU). For these newborns, data on neonatal outcomes is sometimes missing in the maternal clinical record (PIS form), but data can be obtained from records that are kept in the NICU unit. The study will implement a query system to retrieve systematically these data for all deliveries. The data manager using the DMS will produce daily reports, listing all newborns with missing data on neonatal outcomes.

Components of the DMS: Appendix 4 contains the specifications for the development of the software package that will be used to implement data collection procedures at the hospitals level and at CLAP data center. The system will have six modules: Data Entry, Data Validation, Data Transmission, Security, and User Management (Figure 3).

Project secondary outcomes (readiness to change questionnaire to health providers): These data will be collected during baseline and post-intervention (Table 4). A self-administered questionnaire will be used, using paper forms. These forms will be sent to CLAP for data entry.

Process Measures: These will be used to monitor the implementation of the intervention and to assess compliance and protocol violations. A number of different strategies and data collection instruments are going to be used (see table 5).

- Data form, collected by data supervisors that will be sent to CLAP for data entry and validation.
- Monitoring of activities in the web portal, including a system to log the activities of birth attendants and opinion leaders.

9.2. Facilities

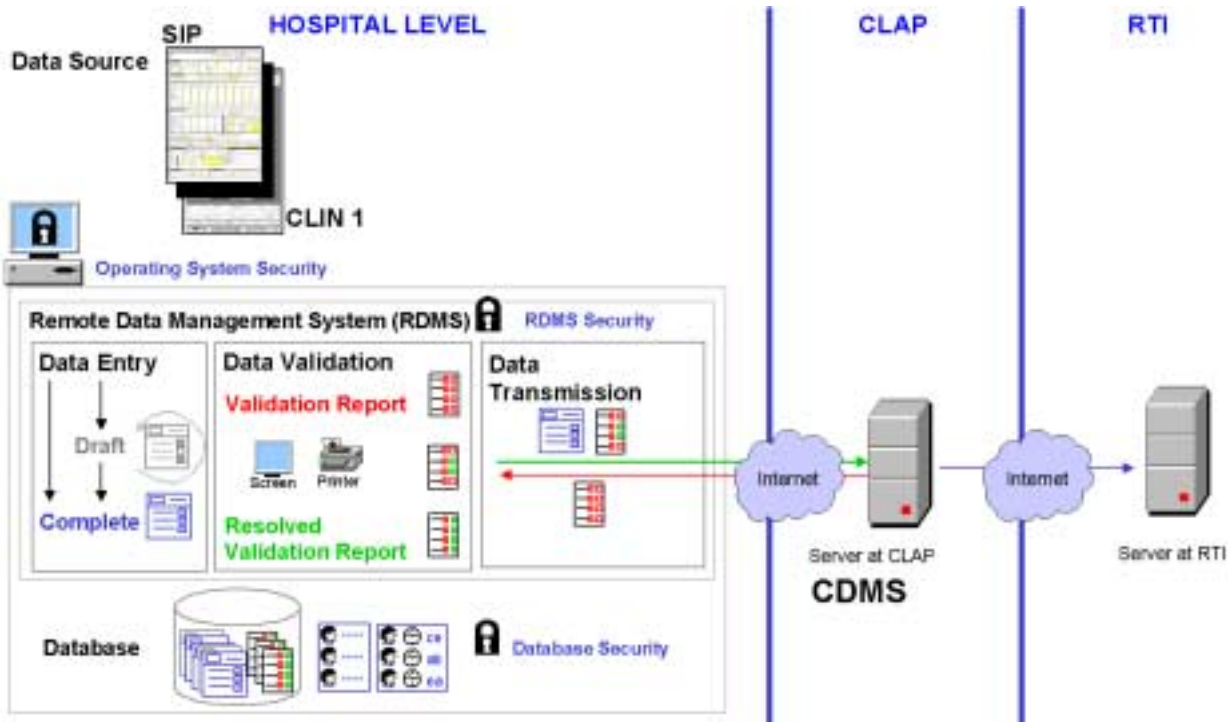
9.2.1. Computer Hardware and Software

Each hospital in the study will have a computer with the DMS installed and access to e-mail (Figure 2). At CLAP headquarters, a server and two terminals will be available for the study, equipped with the full version of the DMS. SPSS statistical software will be used for data analyses. The server will be provided with an uninterruptible power supply (UPS) and a disk array and backup system to assure data integrity.

9.3. Data Entry

Data collection forms (CLIN1, CLIN2, ALTA1 and ALTA2) are modified PIS forms that incorporate data particular to the study (that is not on the standard PIS) and hide the rest of the data. These forms are generated as a carbon copy of PIS. Every morning, the data clerk at the hospital level will collect all CLIN forms for deliveries of the previous day and all ALTA forms for all women that were discharged from the hospital that day. The data manager will then enter the data in the Remote Data Management Subsystem (RDMS) for that hospital. The RDMS is a standalone application that runs on a personal computer. Consistency checks are performed during data entry and warnings are displayed. The data is checked to make certain that entered values are acceptable, that all required fields are entered, and that items are consistent with other related items in the database. (see Appendix 4 for a detailed description of the DMS).

Figure 3. Data Management System components.



9.4. Data Editing and Error Resolution

The database will incorporate routines for data validation (range and rules). If a validation rule fails during data entry, the data manager will be warned and will have the option to accept the value as correct, enter a new value, or generate an electronic query that can be corrected later. In any case, a validation log will be generated and recorded in the database. The log file will also record when the data was entered and by whom. This log will be used to review and audit the data management process (Appendix 4).

Most of the validation will be performed at the hospital level, using highly interactive procedures. Most problems should be solved while the clinical record is easily available. In most public hospitals in the region, it is very difficult and time consuming to access women's clinical records after the subject was discharged from the hospital. This problem can severely limit data quality because data validation queries produced after discharge are not answered. The present system will be designed in such a way that data entry and validation are performed simultaneously, while the clinical record is still available to check for inconsistencies detected by the program routines.

A second data entry will be performed at CLAP at the end of the data collection periods, and the DMS at CLAP will have a module to compare the first and second data entry to produce a validation report. The system will be designed in such a way that all modification to the database are registered in a log file (tracking). The data clerk at CLAP will review typing mistakes and will update the database, taking into account any updates made by the data manager at the hospital. The data in the log file will be used to this aim.

9.5. Transmission of Data

Data and Validation Reports will be sent using an XML messaging system (Appendix 4) from hospitals to CLAP data center on a daily bases. At CLAP, the data will be reviewed, validated, and stored in backup files. Validated databases will be send to RTI, where the main study database will be held.

9.6. Security

The system provides a secure environment for confidential medical information. Access to the system is limited to authorized individuals. The database is backed up on a regular basis. In addition, information that identifies the patient is stripped from the database when transmitted to CLAP CDD and RTI Data Coordinating Center (DCC). The server containing the study data will be provided with a UPS and a disk array and backup system to assure data integrity. The data center will limit access to CLAP personnel involved in data management and analysis.

9.7. Database Construction

After closing the data collection, transaction files, master files, and validation reports will be reviewed. A final validation of data will be prepared and reviewed carefully. After the final cleaning of the data, several back-up copies of the computer files will be taken in a computer

file suitable for data analyses. RTI will hold and maintain the main study database until the end of the study. After completion of the study, a copy will be send to CLAP and UNC-CH for data analysis.

9.8. Monitoring Data Collection

CLAP data center will produce a number of reports to monitor data quality and trial progress (protocol compliance, quality of data at each center, completeness of data and completeness of women's set of forms, progress of recruitment, adverse event reports, etc.). Data quality control will also include medical record abstraction performed retrospectively. For each 3-month period, 1 day will be selected at random, medical records will be abstracted for all women who delivered that day, and data will be compared to the birth register. This will be performed during monitoring visits that will be made by the coordinating team at least once a year in each hospital.

9.9. Reports

9.9.1. Data Monitoring

During the 3-month data collection periods, the data management unit will produce detailed weekly and monthly data monitoring reports to assess data quality (missing and inconsistent data) and to monitor the number of patients that were included in study. These reports will present overall figures for the whole study and will also be stratified by hospital. These reports will be reviewed by the data manager and the study statisticians at CLAP, and they will be sent to the country data supervisor prior to their scheduled visits to the hospitals. If a severe problem is detected according to the reports, the country data coordinator will be contacted and will schedule a new visit to the center with the problem. A summary of the monthly reports will be also reviewed by CLAP study coordinator and the principal investigator.

9.9.2. Steering Committee

An annual summary report will be produced and sent to the Global Network Steering Committee. This report will include a summary of the annual figures for the following:

- Data Quality
- Protocol Violations
- Adverse Events

The year will be measured from May 1st to April 30th. For details on the contents of each report category, see below.

9.9.3. Data Center

The following reports will be periodically sent to RTI.

Data Quality Reports

After each data collection periods, the data management unit will produce a summary report including

- number of patients that were included in the study in that period;
- missing data rates; and
- inconsistent data rates.

These reports will present overall figures for the whole study and will be also stratified by hospital.

Protocol Violations Report

A specific report will be produced to account for potential protocol violations after each phase of the study or component of the intervention, as follows:

- Pre-randomization delivering of information to hospitals
- Selection of hospitals for randomization
- Presentation of the intervention at the hospitals and selection of opinion leaders
- Workshops
- Dissemination phase
- Implementation phase

The in-service training activities in the control hospitals will be reported simoultaneously.

Adverse Events Report

See section 9.9.5.

9.9.4. NICHD

The same reports that will be sent to RTI will be sent to NICHD.

9.9.5. Adverse Events

Adverse Events in Health Providers (study subjects)

- *Loss of job positions*
- *Malpractice lawsuits*

In case of an event of these types, a report will be produced and sent to the corresponding staff at the Data Center and NICHD, within 7 days of identification.

Adverse Events in Women and Children

Maternal deaths

In case of a maternal death, a report will be produced and sent to the corresponding staff at the Data Center and NICHD, within 2 days of identification.

Neonatal Deaths

A monitoring report on the number of in-hospital early neonatal deaths (up to 7 days of life) and the number of live births in the same period will be produced and sent to the Data Center and NICHD, on a monthly basis.

An annual summary report of the adverse events will be produced and sent to the Global Network Steering Committee.

10. Statistical Analysis

10.1. Analysis Plan

Inference will be primary directed at the cluster (hospital) level. All analyses addressing the study research questions will use the "intention to treat" principle, thus comparing the original intervention group to the original nonintervention group, even if hospitals have withdrawn or shifted to another group. The data will be analyzed in collaboration by CLAP, UNC-CH, and the Global Network Data Center.

10.2. Design Issues

Episiotomy rate and active management rate will be assessed before randomization (baseline) and at the end of the intervention period in all hospitals (Table 4). As a subgroup analyses, the effect of the intervention on episiotomy rate will be assessed on primiparous women. Episiotomy and active management rates will be also measured 1 year after the end of the intervention period to assess the maintenance of the effect of the intervention.

10.3. Sample Size

A preliminary analysis of 1995-98 PIS data from 22 Argentinean hospitals showed a baseline frequency of episiotomies among vaginal deliveries of 42%, with a standard deviation of 11%. To protect against changes in the standard deviation (Lomas et al., 1991), we have based our sample size calculations on a standard deviation of 15%. Thus, we will need 18 hospitals (9 intervention and 9 control) to identify a decrease of episiotomy rates from 40% to 20%, with a 0.05 significance level and a 80% power. Our previous analyses of PIS data have shown that about 25% of deliveries are among primiparae, and 75% among multiparae. A reduction of the general episiotomy rate from 40% to 20% could be achieved by reducing the rate among primiparae from 80% to 40%, and the rate among multiparae from 26% to 13%. The rates after the intervention would be similar to the rates achieved in a previous trial (Argentine Episiotomy Trial Collaboration Group, 1993) and are thus potentially attainable. However, the sample size of 18 hospitals will allow us to identify a smaller decrease of episiotomy rates among primiparae vaginal deliveries, from 80% to 60%, with a 0.05 significance level and a 80% power. Assuming a baseline frequency of perineal sutures among primiparae of 85% with a standard deviation of 15%, our sample size of 18 hospitals will give us a power of 80% to identify a reduction of frequency or perineal sutures to 65%, with a 0.05 significance level.

We expect the use of oxytocin during the third stage of labor to increase from 10% to 50%. However, our sample size will allow us to detect smaller changes. Assuming a baseline frequency of injections of oxytocin of 10% and a standard deviation of 5%, the sample size of 18 hospitals will give us a power higher than 95% to identify an increase of use of oxytocin from 10% to 20%, with a 0.05 significance level. Assuming a baseline PPH incidence rate of 15% and a standard deviation of 5%, the sample size of 18 hospitals will give us a power of

84% to identify a reduction from 15% to 8%, and a power of 56% if the reduction were from 15% to 10%.

Hospitals will start the baseline data collection period before randomization to obtain data that will be used to assess the inclusion criteria (episiotomy and active management rate). If they fulfilled the inclusion criteria, they will then be randomized. A total of 24 hospitals will be included in this initial data collection to protect the study from hospital drop-outs and from the possibility of hospitals not fulfilling the inclusion criteria.

10.4. Interim Analysis and Study Monitoring

NICHD will determine the members of the DSMB that will be responsible for monitoring the project.

10.5. Analysis of Primary and Secondary Hypotheses

At the group level, the primary outcome variable is the percentage of primary and secondary outcomes during the three months following the end of the intervention. Despite having only 12 observations in each arm, since each percentage is based on a large number of births, one can use the Normal approximation to the Binomial distribution, and thus the individual percentages can be assumed to be Normally distributed. This implies that when evaluating the efficacy of the intervention using the mean percentages at the end of the intervention period, the Student's t-test is appropriate and its use is justified. Baseline frequencies will also be presented, and baseline to follow-up ratios will be computed. Mantel Haenszel summary risk ratios combining the individual ratios for each hospital in the intervention group and non-intervention group will be computed. The intervention and non-intervention groups will then be compared at the group level using Student's t-test on the logarithms of the summary risk ratio (Wyatt et al., 1998).

In addition, the data collected at the individual level will be used to explore the potential for confounding of the main effects of the intervention due to imbalances arising from the group randomization. Such multi-level analyses will use mixed model techniques (Littell et al., 1996), also known as hierarchical linear models (Bryk and Raudenbush, 1992). These models account for the clustering effect and the intra-hospital correlation of the women from a given hospital. Furthermore, we will use descriptive statistics and GEE modeling (Diggle et al., 1994) to study the evolution of frequencies of outcomes between the four data collection periods.

For the analysis of provider's "readiness to change", the analysis will include three variables, one assessing "readiness to change" episiotomy, one assessing "readiness to change" management of third stage of labor and one assessing attitude toward changing practice in general. Ordinal scales will be used for the responses. Data will be summarized in terms of medians and interquartile ranges. Non-parametric statistics will be used to compare the pre- and post-intervention differences between the control and intervention groups."

11. Quality Control

11.1. Selection of Study Personnel / Job Descriptions

Data Collection:

Data supervisors will have the responsibility of supervising the data collection made by the data collectors on a weekly basis in each hospital and of sending data from the hospitals to the data center. The different amount of work in Buenos Aires Province (50% instead of 25% in Rosario and Montevideo) is because the hospitals of Buenos Aires are spread in a region and not in one city. Therefore the time to travel between hospitals must be taken into account. One supervisor every four or five hospitals will require a part time job in Buenos Aires Province and only 25% of working time in Montevideo or Rosario. Personnel must be a nurse or midwife, with previous experience in supervision of data collection in research studies, to be qualified for these positions.

Intervention:

The study coordinator at CLAP will be responsible for the general supervision of the implementation of the intervention, implemented at the hospital level by the CLAP country study coordinators (two in Argentina and one in Uruguay).

CLAP country study coordinators will be responsible for the implementation of the intervention at the hospital level. The qualification for these professionals is that they must be a physician with a strong background in obstetrics and clinical research.

11.2. Training Procedures

The study statistician, the programmers and the statistical assistant will train the country data supervisors in the use of the data collection procedures and in the use of the DMS. Hospital data collectors will be trained during the preparatory phase in the pilot hospitals in Argentina and Uruguay by the country data supervisors. The manual of operation for data collection will be the main training material (see section 7).

11.3. Certification Procedures

Data supervisors in Uruguay and Argentina will be trained and certified at CLAP headquarters. Data collection and data management at the hospital level will be performed by hospital personnel that will be hired part-time by the study. These personnel will be trained by the data supervisors, and they will have to pass a standardized certification procedure before the beginning of the data collection. The data supervisors will apply the certification procedures. The certification procedure will be developed at CLAP in collaboration with the UNC-CH biostatistician. In order to be certified, these personnel will need to demonstrate a good working knowledge of the DMS developed for the study, including procedures to assure data quality and patients' confidentiality. These personnel will also be trained in ethical issues

in research with human subjects and will go through the online web training provided by OHRP.

11.4. On-site Monitoring

Each study site (Province of Buenos Aires, City of Rosario, and Uruguay) will have one or two assigned data supervisors. They will not be hospital personnel, and they will not be involved in any other study activity. They will train the data collectors, visit each hospital on a weekly basis, meet with the data collector, review the data collection forms (paper, queries, and electronic forms), and check patient recruitment against hospital logbooks and clinical records (paper and electronic forms).

CLAP data unit will produce a number of reports to monitor data quality and trial progress (protocol compliance, quality of data at each center, completeness of data and completeness of women's set of forms, progress of recruitment, adverse event reports, etc.). Data quality control will also include medical record abstraction performed retrospectively. For each 3-month period, 1 day will be selected at random, medical records will be abstracted for all women who delivered that day, and data will be compared to the birth register. This will be performed during monitoring visits that will be made by the coordinating team at least once a year in each hospital.

Completed intervention-monitoring forms, including process data, will be sent to CLAP on a monthly basis. Copies will be kept in the participating hospitals. The process data will be entered in a database at CLAP. Completed Readiness Questionnaires and questionnaires to hospital directors will be mailed directly to CLAP in prestamped envelopes. Data will be entered in a database at CLAP.

11.5. Site Visits

CLAP and UNC-CH principal investigators, National Institutes of Health (NIH) researchers, and RTI researchers will schedule site visits to the study sites. The timing of these visits still needs to be defined.

11.6. Feedback for Protocol Violations

Processes outcome data will be used to monitor protocol violations. The data center at CLAP will produce reports for protocol violations that will be reviewed by CLAP study coordinator and the study statistician, and they will be distributed to the country coordinators. CLAP country study coordinators will contact team leaders at the hospitals to review protocol violations and establish corrective measures.

12. Sustainability

12.1. Dissemination Plans for Research Findings

Outcomes will be spread as much as possible through the following:

a) Publication in a widely spread first-class journal (e.g., New England Journal of Medicine)

b) Publication (electronic) in the NICHD Web Site

c) Publication in local journals of Latin America

d) Presentation of outcomes to the Pan American Health Organization and the World Health Organization so that it can be spread through the usual methods

e) Presentation in congresses and local, national and international meetings

f) Presentation and discussion of outcomes at the participating hospitals

g) Recording at Cochrane Library

12.2. Processes and Equipment Within Country

The study will provide computer equipment and software to all participating hospitals. This equipment will stay at the hospitals at the end of the study. The web page developed for the study will be maintained by CLAP/UNC-CH at the end of the study to keep their basic functions. Measures will be taken by CLAP to give some degree of support to the network of hospitals, through its health promotion program in the region.

12.3. Plans for Use of Trained Personnel

Participating hospitals will be encouraged to participate in the epidemiological surveillance program at CLAP, and a program coordinator will provide support to the hospitals after the study. This program will monitor perinatal outcomes and quality of care in participating hospitals, using the infrastructure and personnel that participated in the study.

13. Study Organization

13.1. Duties of the Research Units

CLAP will be the coordinating center for the study. The study coordinator based at CLAP will work with three country coordinators. There will be one country coordinator for each of the following regions: The Province of Buenos Aires, the City of Rosario, and the Department of Montevideo. Each country coordinator will supervise hospital data collectors. A data manager and data entry clerks will also be based at CLAP. The U.S. investigators will support the coordination of the study by distance communications and by frequent in-country visits.

The trial will be directed by a Steering Committee including the Principal Investigator, the Senior Foreign Investigator, CLAP study coordinator, the Statistician, Data Manager, one Data Center representative, and one NICHD representative. The Steering Committee will meet annually, or more frequently as needed. The Steering Committee will be informed on a regular basis of the progress of the study and will provide regular feedback to the investigators and CLAP study coordinators.

13.2. Duties of the Data Coordinating Center

The Data Center will provide research support services to the Global Network. These will include establishment and maintenance of a centralized information management system to help the Global Network Research Units collect, edit, store, analyze, publish, and disseminate results from their individual projects as well as from shared research. It will assist the program staff of the NICHD and other cosponsoring NIH Institutes and Centers (ICs) in monitoring research progress and will work to ensure data integrity, accuracy, and accessibility among all Research Unit sites. It will offer technical assistance and analytical support for all sites, as needed. The Data Center will provide particular attention to the needs of developing country sites for the purpose of helping develop and enhance their capacity for data collection and analysis. Initially, the Data Center will support primarily the individual research projects undertaken by Global Network Research Units. However, as the Network becomes more established and the capacity of the Research Units to undertake common protocols is strengthened, the Data Center must be prepared to respond to the needs of shared research projects.

All activities of the Data Center must be closely coordinated with the NICHD Staff Science Coordinator. In support of all research projects undertaken by the Global Network, the Data Center staff will do the following:

- Support the activities of the Network Advisory Group, Steering Committee, and the DSMB through provision of materials/documentation support, meeting planning and logistics, and conference call coordination.
- Provide advice on study design, data collection, data analysis, and publication development to all Global Network research projects.

- Prepare, design, and disseminate operations manuals, data collection forms, databases, and results reporting summaries for Global Network research projects.
- Compile for the Network Advisory Group and Steering Committee, the DSMB, the NICHD, and the other participating NIH ICs site visit reports, monthly and quarterly subject enrollment reports, meeting summaries, quarterly Research Unit performance and progress reports, and other reports as needed.
- Maintain or assure maintenance of high quality databases resulting from any collaborative research, supervise all data collection procedures, and arrange for the most efficient transfer of study data where indicated.
- Ensure that all Global Network sites and investigators fully comply with NIH regulatory requirements, including informed consent, reporting of adverse events, human and animal subject safety and welfare provisions, and the requirements of international collaboration.
- Provide training to all Research Unit site personnel as needed on data management and analysis, quality control, and quality assurance.
- In coordination with the NIH cosponsors, provide periodic on-site monitoring to the Research Units for those studies being performed at that site.

13.3. Duties of NICHD

NICHD Staff Involvement: Staff Science Coordinator, Staff Science Collaborators, and Program Official

The NICHD Staff Science Coordinator will serve as the principal representative of the Institute and NIH and, in consultation with relevant NICHD program staff and representatives of the other NIH cosponsors, will provide overall programmatic oversight, coordination, and assistance to the Global Network. Specifically, the NICHD Staff Science Coordinator will do the following:

- Facilitate communication, cooperation, and the exchange of information among network members and between the network components and other existing programs to support collaborative efforts.
- Participate as a voting member of the Steering Committee.
- Consult with NICHD program staff and cosponsoring NIH ICs, who may be designated as staff science collaborators assigned to specific studies, when needed for optimal implementation of study designs.
- Assist the Steering Committee in the selection and approval of research topics and the development and review of protocols for any specific studies.
- Together with the Steering Committee chairperson, approve formation and membership of any Steering Committee subcommittees.
- Oversee site participation and performance with the support of the Data Center.
- Participate in study design, data analysis, interpretation, and publication of study results.

NICHD Staff Science Collaborators

Other NICHD staff may be assigned as staff science collaborators for Network grants assigned to them in their areas of scientific expertise. They may participate in Steering Committee meetings as non-voting members. Specifically, the NICHD Staff Science Collaborators will, in consultation and collaboration with the NICHD Staff Science Coordinator, do the following:

- Provide programmatic oversight and assistance to awardees assigned to the NICHD.
- Provide advice, when needed, for optimal implementation of intervention designs.
- Assist in overseeing site participation and performance, as needed, with the support of the Data Center.
- Participate, as needed, in study design, data analysis, interpretation, and publication of study results relevant to the research conducted by their respective grantees.

NICHD Program Official

NICHD will designate a Program Official, who will assume the administrative stewardship responsibilities and obligations for the Global Network.

14. Human Subjects

14.1. Description of Participants

Birth attendants from 24 hospitals will be the subjects of this research. We expect the number of birth attendants to vary between 10 and 30 per hospital. They will be MDs, midwives, nurses, or other health professionals. Birth attendants will all be age 18 or older. There will be no exclusion based on sex, minority status, or other criteria.

14.2. Recruitment

Birth attendants from 24 hospitals will be included in the study. The recruitment will take place at the hospital level, and all birth attendants will be offered to participate. There will thus be equal access to participation among women and minorities. In Argentina, we will recruit hospitals in the province of Buenos Aires and the city of Rosario. In Uruguay, we will recruit hospitals in the Department of Montevideo. Hospitals will be recruited CLAP. CLAP will contact potential participants among hospitals affiliated to the Center or already collaborating with it.

14.3. Informed Consent

Formative Research

All focus group participants will be asked to provide informed consent (Appendix 5). The informed consent form will be read aloud to the group to ensure that any patients with reading difficulties understand and can knowledgeably respond to the form.

Intervention

Hospital responsible authority (director or medical head) will provide written consent to participation before randomization (Appendix 5). Individual health providers will receive a fact sheet describing the objectives of the study and including the name and phone number of the country coordinator (Appendix 5).

Birth attendants in the intervention hospitals will receive a fact sheet (Appendix 5) that provides them with information as to the format, length, and purpose of the training intervention; any benefits or risks they might incur as participants; their right to decline to participate without retribution; who to contact in case they have questions or concerns; and the fact that they will be informed of the results of the study. Birth attendants selected as opinion leaders in the intervention hospitals will provide written consent to accept that role in the implementation of the intervention (Appendix 5).

14.4. Incentives and Other Benefits

Formative Research

Light refreshments will be provided during the focus groups.

Intervention

Each participating hospital will receive a personal computer. The intervention hospitals will receive it at the beginning of the intervention. The control hospitals will receive it after the intervention.

14.5. Cultural Issues

To ensure that materials and interventions are effective, culturally appropriate, and readily integrated into routine care, we will conduct three focus groups, of 8 to 10 participants each, in each country: one with obstetricians, one with midwives and nurses, and one with patients. The focus groups will be conducted outside the catchment's area for the study. The goal of the focus groups with physicians and with midwives and nurses is to refine all hospital-based intervention materials (e.g., reminders, training manuals, etc.). They will also assist us in developing and refining systems for integrating the intervention materials into the hospitals (e.g., process of identifying a coordinator within the hospital, scheduling in-service training and follow-up meetings). They will be asked to advice on the appropriateness of the survey instrument and the acceptability of the skills training program. Various educational tools such as lecture format and written materials will be presented to assess the acceptability of each. The focus group with patients will assist us in developing recommendations on women's involvement in the clinical decision process.

14.6. Reporting to Local IRBs

This project has been reviewed and approved by the Institutional Review Boards (IRBs) of the following institutions: The Argentinean Society for Clinical Research, Argentina; The Faculty of Medicine, Universidad de la Republica, Uruguay; The School of Public Health at UNC-CH, USA; and The Pan American Health Organization.

During the trial, IRBs will receive the following reports:

- Annual Progress report
- Serious Adverse events reports

15. Publications and Presentations

The review process and authorship for publications and presentations will follow the guidelines set forth in the Policy and Procedures Manual of the Global Network for Women's and Children's Health Research. Any submission for publication or for presentation at professional conferences must adhere to these principles.

15.1. Review Process

Prior to their submission or application for presentation, all manuscripts, posters or oral presentations, or other reports of the outcomes of this research effort must be approved by a majority of the members of the Site 1 Steering Committee. This committee's membership includes (1) the Principal Investigator, (2) the Senior Foreign Investigator, (3) the NIH Project Officer, (4) a Senior Research Officer from the Data Center, (5) the Study Coordinator, and (6) the Statistician and Data Manager.

15.2. Authorship

The authorship of manuscripts, poster or oral presentations, or other reports of the results of this study will be guided by the criteria for authorship formulated by the International Committee of Medical Journal Editors and published in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals (updated October, 2001; available at http://www.icmje.org). According to these criteria, the authors should meet the following criteria.

Each author should have participated sufficiently in the work to take public responsibility for the content. Authorship credit should be based only on substantial contributions to (a) conception and design, or analysis and interpretation of data; and to (b) drafting the article or revising it critically for important intellectual content; and on (c) final approval of the version to be published. Conditions (a), (b), and (c) must all be met.

As a multicenter study, up to 12 authors, as permitted by journals such as the New England Journal of Medicine and the American Journal of Obstetrics and Gynecology, may be identified for a given manuscript, but only those authors fulfilling the criteria above are eligible. As a general, but not absolute, rule, at least one individual from the NIH, one individual from the Data Center, the U.S. Principal Investigator, and the Senior Foreign Investigator will be authors for all publications that result from this research.

All publications, posters, oral presentations at scientific meetings, seminars, and any other forum in which results of this NICHD-supported research are presented will include a formal acknowledgement of NICHD support, citing the NIH grant number as identified on the award document.

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17. Appendix 1

Summary Of The Different Organizational Charts And Characteristics Of The Preselected Hospitals In Argentina And Uruguay

See attached file "GN-SITE1-Protocol-v8.0-Appendix1 – Hosp Chars.doc"

18. Appendix 2

Web Portal:
Management of scientific-technical information sources

See attached file "GN-SITE1-Protocol-v8.0-Appendix2 - Web portal.doc"

19. Appendix 3

Formative Research Protocol

See attached file "GN-SITE1-Protocol-v8.0-Appendix3 – Frm Rsr.doc"

20. Appendix 4

Data Management System Specifications

See attached file “GN-SITE1-Protocol-v8.0-Appendix4 - DMS Spec.doc”

21. Appendix 5

Informed consent forms

See attached file “GN-SITE1-Protocol-v8.0-Appendix5 - Consents.doc”

22. Appendix 6

Data collection forms

See attached file "GN-SITE1-Protocol-v8.0-Appendix6 - Data Forms.doc"