

Request for Proposals 2009-075

Determining the effect and safety of prophylactic administration of oxytocin in Uniject™ by Auxiliary Nurse Midwives on postpartum hemorrhage in Karnataka, India

I. Summary of Deadlines

Release of request for proposals	October 12, 2009
Confirmation of interest due	October 16, 2009
Fact-finding questions due	October 23, 2009
Response to fact-finding questions	October 30, 2009
Proposals due	November 5, 2009
Identification of short-listed organizations	November 11, 2009
Interview period for short-listed organizations	November 16-17, 2009
Notification of results	November 20, 2009

PATH reserves the right to modify this schedule as needed. All parties will be notified of any deadline changes simultaneously by email.

II. PATH Statement of Business

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act. PATH's work improves global health and well-being.

Headquartered in Seattle, Washington, PATH has 33 offices in 19 countries. PATH currently works in more than 70 countries in the areas of health technologies, maternal and child health, reproductive health, vaccines and immunization, and emerging and epidemic diseases.

For more information, please visit www.path.org

III. Project Background and Introduction

Over 500,000 women die of childbirth and pregnancy-related causes each year. Postpartum hemorrhage, defined as blood loss of 500 ml or more, is the largest cause of maternal deaths globally (Ronsmans and Graham 2006). Despite the large percentage of maternal deaths attributed to postpartum hemorrhage, it is the only obstetric complication with an effective preventive intervention. Active management of the third stage of labor (AMTSL), a package of interventions generally defined as administration of a uterotonic immediately following birth, controlled cord traction and uterine massage following delivery of the placenta, is recommended by the World Health Organization (WHO) for the prevention of postpartum hemorrhage. This intervention has been proven to reduce postpartum hemorrhage in hospital based births (Prendiville, Elbourne et al. 2000).

Given that approximately half of all births take place at home in low-income countries, researchers have explored means of adapting active management of the third stage of labor for use in home-based births. The approach for such an intervention must consider both the skill level of the provider and the uterotonic drug to be used. Recent recommendations from the WHO relevant to these two issues are summarized below:

- There are no trial data to recommend or discourage use of active management of the third stage of labor by non-skilled birth providers. There is, however, substantial concern regarding the risk of uterine rupture that could result from inappropriate cord traction, for example. Consequently, the WHO does not recommend active management by non-skilled workers.
- Skilled birth attendants should offer oxytocin in preference to injectable ergometrine/methylethergometrine or oral or sublingual misoprostol to all women for postpartum hemorrhage prevention.
- Given recommendations against active management of the third stage of labor to prevent postpartum hemorrhage by non-skilled workers, in the absence of active management, oxytocin or misoprostol should be given by a health worker *trained in its use* to prevent postpartum hemorrhage.

Given that oxytocin is the preferred drug for postpartum hemorrhage prevention, questions arise regarding the safety and effectiveness of lower level health care providers administering injectable oxytocin at home births. There are no data to support or discourage the use of injectable uterotonics to prevent postpartum hemorrhage by lower level health care providers. The Technical Consultation on Postpartum Hemorrhage, convened by WHO in Geneva in October 2006 highlighted the need for appropriately designed studies to address this question among their research priorities.

Three issues are of concern regarding the use of oxytocin for postpartum hemorrhage prevention at home; 1) the drug requires refrigeration, 2) the drug requires administration via injection,

which in many countries requires a medical professional, and 3) the drug may be used inappropriately prior to delivery of the baby to start or accelerate labor.

Oxytocin in Uniject™ with a time/temperature indicator alleviates many of the barriers associated with the first two concerns. Uniject™ is a drug delivery device that assures accurate dosage with a non-reusable needle (PATH 2009). It has been used extensively and safely by non-medical personnel in vaccination campaigns in low income countries and a study in Mali showed that midwifery assistants were able to use oxytocin in Uniject correctly following a training intervention (Combary, Traore et al. 2008). The time/temperature indicator is a sticker adhered to each individual pouch containing the Uniject™ device which changes colors when the drug becomes chemically inactive due to cumulative heat exposure (PATH 2008). With access to some refrigeration or even coolers, it is now feasible to consider using oxytocin in Uniject™ in a broader array of settings, including where frequent re-supply is not feasible.

Use of any intramuscular oxytocic before the birth of the infant is regarded as dangerous because the dosage cannot be adapted to the level of uterine activity, as is possible with the monitored administration of intravenous oxytocin in health facilities (WHO 2000). Hyper-stimulation of the uterus may result from an injection of intramuscular oxytocin and can lead to uterine rupture, fetal asphyxia or fetal demise (Konje, Odukoya et al. 1990; Zheng and Zhang 1994).

Inappropriate use of oxytocin injections to induce and particularly to accelerate labor during home births is well documented in some parts of the world. Descriptive reports published in the medical and social science literature indicate that this practice is common in South Asia. A recent literature review of uterotonic use at home births (Flandermeyer, Stanton et al. 2009) included reports indicating that from 1 to 69 percent of women delivering at home receive oxytocin injections to accelerate labor in India and Bangladesh (Fronczak, Antelman et al. 2005; Matthews, Ramakrishna et al. 2005; Sharan, Strobino et al. 2005; Jeffery, Das et al. 2007). A number of small-scale ethnographic studies have also documented this practice in India (Iyengar, Iyengar et al. 2008; Van Hollen 2003). A recent government policy which recommends that Auxiliary Nurse Midwives (ANMs) at peripheral (non-surgical) health facilities should administer oxytocin injections during the third stage of labor to treat postpartum hemorrhage has raised concerns that this policy shift could readily reinforce the practice of inappropriate intra-partum oxytocin use. Additional research on the safety and efficacy of providing oxytocin for postpartum hemorrhage prevention for use by low-level cadres in peripheral health settings should be conducted and evaluated (Jeffery, Das et al. 2007).

IV. Scope of Work and Deliverables

A. Scope of Work

PATH and the Johns Hopkins Bloomberg School of Public Health, with funding from the Bill & Melinda Gates Foundation (BMGF) have undertaken the Oxytocin Initiative to explore the expansion of oxytocin to trained health care cadres (lower level health care providers) for the prevention of postpartum hemorrhage in peripheral health facilities and home-based births. The Oxytocin Initiative has two components: a community-based, randomized controlled trial to assess the effectiveness and safety of this intervention to reduce the risk of postpartum hemorrhage in Karnataka, and the development of a landscape review report which explores the

use of uterotonics at or around birth in India. *With this RFP*, we ask interested applicants to outline an appropriate study design for the community-based trial. Cost estimates, staffing requirements and a timeline for implementation of the trial should also be submitted as part of the proposal. Applicants are asked to follow the proposal format presented in appendix A and cost format per appendix C.

Details regarding the trial

The trial should be designed to test the hypothesis that administration of oxytocin via the Uniject device during the third stage of labor by Auxiliary Nurse Midwives (ANMs) attending births at home or at the sub-centre level will reduce the risk of postpartum hemorrhage by 50% relative to deliveries attended by the same type of providers who do not provide the intervention drug. (For detailed information on the Uniject device, see appendix B.) PPH prevention is the primary objective of this trial and postpartum hemorrhage is the primary outcome. Assessing safety is a secondary objective. Safety of this intervention is defined as mistimed use of uterotonics, that is, use of uterotonics prior to the delivery of the baby. Possible outcomes of unsafe use could include: fetal death, birth asphyxia/ newborn resuscitation, low APGAR score, postpartum hemorrhage, uterine rupture and referral and transport of the mother to higher care. Interventions to increase effectiveness and safety of the intervention must include ANM training on the use of oxytocin via Uniject for PPH prevention.

Given the well documented history of inappropriate use of uterotonics to accelerate labor, in proposing a design for this trial applicants might also consider additional and innovative interventions which address demand-side issues such as maternal/family request for labor augmentation, community education regarding the dangers of inappropriate uterotonic use and the role of the village drug seller. A three arm trial may be one option to consider. Safety and/or maternal/fetal adverse outcomes due to lack of safety represent a secondary outcomes of this study.

To assist in the development of feasible proposals, please note that the sample size for the trial should fall between 1500 and 2000 births and field work should be completed within 12-18 months.

B. Deliverables

The institution/organization contracted to conduct a community-based trial in Karnataka will be responsible for the deliverables listed below. Therefore, all proposals submitted in response to this RFP should address plans to achieve the following:

1. Provide research protocol(s) to be finalized in collaboration with JHSPH and PATH counterparts. Protocols should detail research design and rationale, questions under study, study populations and sampling frame, including selection procedures, consent and ethics, description of data collection method and content, outline of data management/analysis plan, list of study activities including training of research team and field research staff, timeline and complementary reference list;
2. Obtain all necessary ethical approvals for trial implementation;

3. Develop and finalize all data collection tools required for implementation of the research trial
4. Develop and finalize a data reporting and management plan, including procedures for database development, data storage and quality assurance measures. All submissions should address data security and confidentiality.
5. Work collaboratively with Johns Hopkins Bloomberg School of Public Health staff on data analysis of the trial;
6. Collaborate with PATH and the Johns Hopkins Bloomberg School of Public Health to disseminate the results of the trial through various avenues;

V. Costs

Provide itemized costs for the proposed trial based on the scope of work outlined in Section IV. The final scope of work may be subject to negotiation; however, evaluation of submissions will be conducted using the originally proposed budget. The budget should be submitted in both Indian rupees and US dollars. A budget narrative including data to support actual costs and/or methodologies to support cost estimates for all major line items listed in the budget should be provided. A template containing major line items is contained in appendix C.

Direct Research Costs

This section of the budget proposal should indicate and justify the remuneration requested. Research expenses encompass services and materials required to carry out the research. Research expenses may include remuneration to research assistants, vehicle hire, consumable goods or non-capital equipment such as photocopier supplies, maintenance of research equipment, computer services and local travel.

a. Personnel Costs: a1: For each person (or category of personnel), specify the exact activity the person will be working on, the amount of days spent and what total salary this represents for each person. Separately list any consultants used.

b. Travel and Transportation: Indicate modes of travel, estimated number of trips, cost per trip (transportation and expenses or per diem), and number of travel days per trip. Include local travel expenses such as gasoline and mileage, vehicle hire etc.

c. Workshop and Training: This budget category includes the cost of project-related training organized by the recipient. Include the number of interviewers or participants (ANMs) for Uniject training, their rates and the number of expected training days. List the cost of the venue and vehicle(s) to be hired and the per diems for each person.

d. Project Supplies and Equipment: The budget should include an estimate for the printing of training materials and documents and list costs incurred for the printing and distribution of the final report as well. This estimate can also include a modest amount for IT, graphics, and equipment.

e. Dissemination: The budget should include estimates of costs related to dissemination of the research findings following implementation of a trial.

f. Other Direct Project Costs: This budget category should only encompass those administrative costs that are not directly related to research. They may include items such as general office expenses or communication and postage expenses.

Indirect Costs

Indirect costs are overhead expenses incurred as a result of the project but not easily identified with the project's activities. These are administrative expenses that are related to overall general operations and are shared among projects and/or functions. Examples include executive oversight, accounting, grants management, legal expenses, utilities, and facility maintenance.

Indirect rate allowances: These rates are maximum amounts allowed by PATH under BMGF funded projects. If the organization has lower rates, the lower rates should be used. To the extent that indirect costs are applicable, they are subject to the following limits:

- Up to 10% for U.S. universities and other academic institutions.
- Up to 15% for non-U.S. academic institutions, and all private, voluntary, and nongovernmental organizations, regardless of location.
- No indirect costs will be paid to U.S. Government agencies.
- Rates apply both to the primary grantee, sub-grantees, and subcontracts that are part of the proposal.

Please note that to the extent possible, identifiable (allocable) costs should be documented and justified in the proposal as direct costs, including those for dedicated ongoing project management, facilities, and support.

VI. Overall Qualifications

Please provide the following information regarding the qualifications of your organization:

- A profile of relevant corporate qualifications;
- A profile detailing professional experience in the context of public health;
- Qualifications of key members of the proposed project team (please provide CVs for all proposed personnel and details of back-up/standby teams);
- Number of years in business;
- Annual revenue;

If your organization has multiple locations, please indicate these qualifications for the site that is responding. Organizations must provide complete contact information for the location responding.

VII. Proposal Evaluation Criteria

Proposals will be assessed based upon the criteria listed below. All proposals will be evaluated by a team from PATH, the Johns Hopkins Bloomberg School of Public Health and select members of the local Technical Advisory Group.

- Submitted proposals will be evaluated based on the technical quality and creativity of the design proposed to address the research questions outlined in this RFP document. Proposals should illustrate the team's knowledge, experience and a clear plan for accomplishing the deliverables.
- Experience of the project team, and overall relevant corporate experience;
- Capacity to perform the work within the desired timeline;
- Propriety and cost effectiveness of budget, as well as the level of cost detail provided;
- Demonstrated knowledge of quality control mechanisms
- Institution's experience with obtaining Health Ministry Screening Committee (HMSC) approval
- Responsiveness to this RFP

PATH reserves the right to disqualify proposals that are not responsive or that do not illustrate sufficient technical knowledge.

VIII. Instructions for Responding

A. Confirmation of Interest

Please send a statement acknowledging receipt of this solicitation and your intent to respond no later than **October 16, 2009** to Ms. Patricia Boison (pboison@path.org) and copied to Mr. Keith Neroutsos (kneroutsos@path.org).

B. Fact-finding Questions

All questions regarding this RFP must be provided in English and in writing no later than **October 23, 2009** to ensure that responses can be provided in a timely manner. These questions should be addressed to Ms. Patricia Boison (pboison@path.org) and copied to Mr. Keith Neroutsos (kneroutsos@path.org). Responses to all inquiries will be provided by **October 30, 2009**. Please note that responses will not be confidential except in cases where proprietary information is involved. Inquiries after this date cannot be accommodated. Bidders must provide an email contact in order to receive the responses.

C. Proposal Submission

Completed proposals should be received no later than **close of business, 17:30 hours, November 5, 2009**. Note that both hard copies and electronic copies are required.

An electronic copy of the proposal submission should be directed to Ms. Patricia Boison (pboison@path.org) and copied to Mr. Keith Neroutsos (kneroutsos@path.org).

Please direct hard copies to:

Mr. Nitya Nand Deepak
Research Coordinator, Oxytocin Initiative
PATH
A-9, Qutab Institutional Area
New Delhi 110067

Please send electronic submissions as Microsoft Word or PDF files. PATH will not accept responsibility for resolving technical transmission problems with proposals. Submission content should be limited to information pertaining to the scope of work described in this RFP. Any information submitted outside of the proposal requirements will be reviewed at PATH's discretion.

D. Selection of Short-Listed Applicants

PATH reserves the right to select a short-list of applicants based upon the qualifying information detailed in section VI. PATH has the option to interview and discuss specific details of the submitted proposals with short-listed candidates. All organizations submitting proposals for consideration should have representatives available during the interview period (**November 16-17, 2009**). All applicants selected for an interview will be contacted by PATH.

E. Notification of Results

Applicants will be notified of PATH's decision by **November 20, 2009**. The final award is subject to the terms and conditions included in this solicitation, as well as successful final negotiations of all applicable terms and conditions affecting this work.

IX. Terms and Conditions of the Solicitation

A. Notice of Non-Binding Solicitation

PATH reserves the right to reject any and all bids received in response to this solicitation, and is in no way bound to accept any proposal.

B. Confidentiality

All information provided by PATH as part of this solicitation must be treated as confidential. In the event that any information is inappropriately released, PATH will seek appropriate remedies as allowed.

Proposals, discussions, and all information received in response to this solicitation will be held as strictly confidential, except as otherwise noted.

C. Communication

All communications regarding this solicitation shall be directed to appropriate parties indicated in Section VIII. Contacting third parties involved in the project, the review panel, or any other party may be considered a conflict of interest, and could result in disqualification of the proposal.

D. Acceptance

Acceptance of a proposal does not imply acceptance of its terms and conditions. PATH reserves the option to negotiate on the final terms and conditions. We additionally reserve the right to negotiate the substance of the finalists' proposals, as well as the option of accepting partial components of a proposal if appropriate.

E. Right to Final Negotiations

PATH reserves the option to negotiate on the final costs and final scope of work, and also reserves the option to limit or include third parties at PATH's sole and full discretion in such negotiations.

F. Third-Party Limitations

PATH does not represent, warrant, or act as an agent for any third party as a result of this solicitation. This solicitation does not authorize any third party to bind or commit PATH in any way without our express written consent.

G. Proposal Validity

Proposals submitted under this request shall be valid for 90 days from the date the proposal is due. The validity period shall be stated in the proposal submitted to PATH.

X. References

- Combarry, P., D. Traore, et al. (2008). Final assessment on the feasibility of auxiliary midwives using the Active Management of the Third Stage of Labor (AMTSL) in Mali, United States Agency for International Development (USAID).
- Flandermeyer, D., C. Stanton, et al. (2009). Uterotonic Use in Home Births in Low-income countries: A Structured Literature Review.
- Fronczak, N., G. Antelman, et al. (2005). "Delivery-related complications and early postpartum morbidity in Dhaka, Bangladesh." International Journal of Gynecology and Obstetrics **91**: 271-278.
- Iyengar, S. D., K. Iyengar, et al. (2008). "Childbirth practices in rural Rajasthan, India: implications for neonatal health and survival." Journal of Perinatology **28**: S23-S30.
- Jeffery, P., A. Das, et al. (2007). "Unmonitored Intrapartum Oxytocin Use in Home Deliveries: Evidence from Uttar Pradesh, India." Reproductive Health Matters **15**(30): 172-178.
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- Mathai, M., A.M. Gulmezoglu, et al. (2007). "Saving women's lives: evidence-based recommendations for the prevention of postpartum haemorrhage." Bulletin of the World Health Organization **85**(4): 322-323.
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- Rawal, A. (2003). "Continuing Medical Education: Trends in Maternal Mortality and Some Policy Concerns." Indian Journal of Community Medicine **28**(1): 43-46.
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- Van Hollen, C. (2003). "Invoking vali: painful technologies of modern birth in South India." Medical Anthropology Quarterly **17**(1): 49-77.
- WHO (2000). Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors. Geneva, World Health Organization.
- Zheng, Q. L. and X. M. Zhang (1994). "Analysis of 39 cases of maternal deaths caused by incorrect use of oxytocin." Zhonghua Fu Chan Ke Za Zhi **29**(5): 276-277.

Appendix A. Outline for Proposal Submission

Study Title: Determining the effect and safety of prophylactic administration of oxytocin in Uniject™ by Auxiliary Nurse Midwives on postpartum hemorrhage in Karnataka, India

The proposal should be no more than 25 single-spaced typed pages, excluding CVs and other reference materials, which may be included as annexes. The proposal should include the following sections:

1. Research Question and Aims

- a. Primary objective
- b. Secondary objectives/aims

2. Background and rationale for this study in Karnataka

3. Participants

- a. Identify Study participants and the population:
- b. Inclusion/exclusion criteria:
- c. Sample size estimate and justification

4. Study procedures:

- a. General study design and methods
- b. Study procedures, including their sequence and timing
- c. Expected duration of the study
- d. Randomization

5. Risks

6. Benefits

7. Recruitment process

8. Consent process and documentation

9. Data processing procedures and confidentiality

10. Expected results and dissemination plan

- a. Expected results should be specified and may include:
 - the solution of specific problems upon which the research has focused;
 - new knowledge in the scientific area under inquiry;
 - policy formulation and/or implementation;
 - methodological development in the field of inquiry
- b. This section should also describe the ways in which the project's findings will be disseminated. Some ideas include seminars or potential publications.

11. Timeline

This section should include a schedule of activities for the duration of the project.

12. Budget

The budget should be submitted per appendix C in both Indian Rupees and U.S. Dollars. A budget narrative justifying all major line items should accompany the budget proposal

Appendix B. Information on the Uniject device

History of the Uniject Device

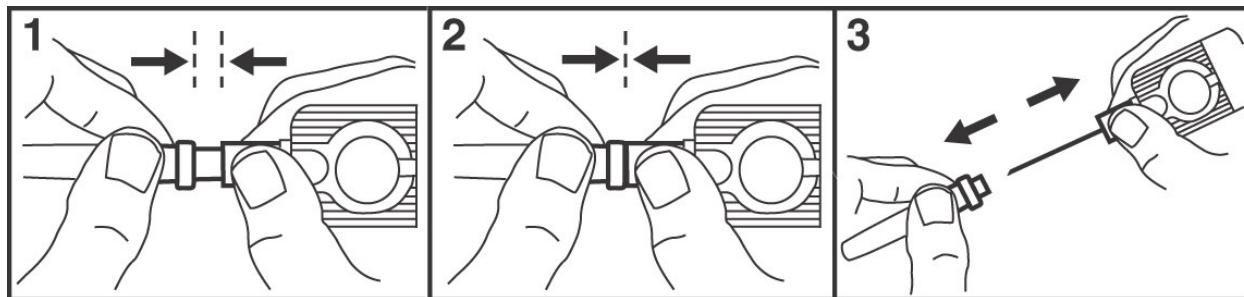
A decade ago, prefilled syringes were too costly for use in public-sector health programs, and no prefilled syringe on the market offered an auto-disable feature. With support primarily from the United States Agency for International Development (USAID), under the Technologies for Health (HealthTech) project, and guidance from the World Health Organization (WHO) and a multitude of other collaborators, PATH developed an auto-disable, prefilled syringe known as the Uniject[®] device. Today, the Uniject device is licensed to Becton Dickinson (BD), the world's largest manufacturer of injection equipment, for commercial production and distribution. This report provides an update to public-sector agencies on the status of the Uniject device.



Description of the Uniject Device

The Uniject device is a prefilled, single-dose injection device specifically designed to prevent attempts at reuse. It combines drug or biological, syringe, and needle packaged in a sealed foil pouch. Uniject devices are available in 0.25-, 0.5-, and 1.0-ml dose sizes and can be ordered with any standard needle size.

Instructions for Using the Uniject Device



Rationale for the Uniject Device

The Uniject device was designed with the following features in mind:

- ✓ **Single dose** – to minimize wastage and facilitate outreach to individual patients
- ✓ **Prefilled** – to ensure that the correct dose is given, and to simplify procurement and distribution logistics
- ✓ **Nonreusable** – to minimize patient-to-patient transmission of bloodborne pathogens
- ✓ **Easy-to-use** – to allow self-injection and use by health workers who do not normally give injections, and to facilitate use in emergency situations
- ✓ **Compact size** – for easy transport and disposal

Appendix C. Budget Template

Please see section V of this document for a detailed description of the costs listed below.

Detailed Project Budget					
S. No.	Major Line Items	Unit	Rate	Total Budget (INR)	Total Budget (USD)
A1	Personnel				
	salary				
A2	Consultants				
	honorarium				
B	Travel and Per Diem				
C	Workshop and Training costs				
D	Project Supplies and Equipment				
E	Dissemination costs				
F	Other Direct Project Costs				
	TOTAL DIRECT COSTS				
G	Indirect Costs (rate and total)				
	TOTAL				