



# PRE-EMPT

Pre-eclampsia and eclampsia  
monitoring, prevention & treatment



# PRE-EMPT ANNUAL REPORT 2016-17







PRE-EMPT ANNUAL REPORT

**2016-17**



ABOVE: An antenatal clinical in a primary health centre in Ogun State, Nigeria.

# Table of Contents

<b>Acronyms</b>	<b>vi</b>
<b>Introduction &amp; Overview</b>	<b>ix</b>
<b>Objective 1: Prevention</b>	<b>1</b>
The CAP (Calcium And Pre-eclampsia) Trial: A WHO Collaboration	2
<b>Objective 2: Monitoring</b>	<b>9</b>
Monitoring Timeline	10
miniPIERS (Pre-eclampsia Integrated Estimate of RiSk)	12
Community Blood Pressure Monitoring in Rural Africa and Asia: the Detection of Underlying Pre-eclampsia and Shock (CRADLE)	13
Maternal Mortality and Maternal Morbidity	16
Pulse Oximetry	18
PIERS on the Move: Transitioning from Pre-eclampsia to Pregnancy and Neonatal Care	21
Mapping Outcomes for Mothers (MOM)	23
fullPIERS (Pre-eclampsia Integrated Estimate of RiSk): External Validation, Recalibration and Added Value of a Novel Biomarker	26
Collaborative Integrated Pregnancy High-Dependency Estimate of Risk (CIPHER)	28
Placental Growth Factor in Mozambique	30
Extension of the fullPIERS model with Placental Growth Factor (PIGF) for Prognosis in Women with Pre-eclampsia	33
Economic Evaluation of the CLIP Trials	35
<b>Objective 3: Treatment</b>	<b>39</b>
Treatment Timeline	40
Gynuity Health Projects Oral Antihypertensive Trial	42
Community Level Interventions for Pre-eclampsia (CLIP) Trials	44
A Randomised Controlled Trial of Sildenafil Therapy in Dismal Prognosis Early-Onset Intrauterine Growth Restriction (STRIDER) Trials	57
Control of Hypertension in Pregnancy Study (CHIPS) Trial	59
<b>Objective 4: Collaboration</b>	<b>63</b>
Collaboration Timeline	64
The Global Pregnancy Collaboration (CoLab)	66
The PRECISE (PREgnancy Care Integrating Translational Science, Everywhere) Network: a Sub-Saharan Network for Placental Disorders	75
TraCer Project	76
<b>Objective 5: Knowledge Translation</b>	<b>79</b>
The Preeclampsia Foundation	80
GLOWM Safer Motherhood App Resource for Mobile Phones	85
Magnesium Sulphate for Fetal Neuroprotection of the Preterm Infant (MAG-CP)	86
PRE-EMPT Advocacy, Global Access, and Select Publications	88
Joint ISSHP/ISOM Global Health Committee	89
<b>Appendices</b>	<b>95</b>
Appendix A	96
Appendix B	105
Appendix C	111

# Acronyms

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ACT	All Children Thriving
AIC	akaikae information criterion
APACHE	Acute Physiology and Chronic Health Evaluation
aPTT	activated partial thromboplastin time
ANM	auxiliary nurse midwife
ANOVA	analyses of variance
ASHA	accredited social health activists
ASSIST	Applying Science to Strengthen and Improve Systems
AUC ROC	area under the receiver operating characteristic curve
AWARE	Angiogenic Factors Will Assist in Risk Evaluation
BCCHR	BC Children's Hospital Research Institute
BJOG	British Journal of Obstetrics and Gynaecology
BMC	BioMed Central
BP	blood pressure
BWF	Burroughs Wellcome Fund
CAP	Calcium and Pre-eclampsia
CDC	Centers for Disease Control and Prevention
CHAI	Clinton Health Access Initiative
CHERRY	Chronic Hypertension and L-citrulline Study
CHIPS	Control of Hypertension in Pregnancy Study
CHW	community health worker
CIHR	Canadian Institutes of Health Research
CIPHER	Collaborative Integrated Pregnancy High-Dependency Estimate of Risk
CISM	Manhiça Health Research Centre
CISMAC	Centre for Intervention Science in Maternal and Child Health
CLIP	Community Level Interventions for Pre-eclampsia
CNFUN	Canadian Neonatal Follow-up Network
CNPq	National Council of Scientific and Technological Development
CoLab	The Global Pregnancy Collaboration
CPN	Canadian Perinatal Network
CRADLE	Community Blood Pressure Monitoring in Rural Africa and Asia: Detection of Underlying Pre-Eclampsia
CRADLE VSA	Vital Signs Alert
cRCT	cluster randomized control trial
DALYs	disability-adjusted life years
EMPOWER	Empowering Progress in Obstetric and Women's Health Research
FINNPEC	Finnish Pre-eclampsia Consortium
GIS	geographical information systems
GMC	Government Medical College
GSK	GlaskoSmithKline
HDP	hypertensive disorders of pregnancy
HELLP	hemolysis, elevated liver enzymes, and low platelet count
HIC	high-income countries
HSK	Hanagal Shree Kumareshwar
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IECS	Instituto de Efectividad Clínica Sanitaria
INFANT	Irish Centre for Fetal and Neonatal Translational Research
IPV	intimate-partner violence
ISOM	International Society of Obstetric Medicine
ISSHP	International Society for the Study of Hypertension in Pregnancy
iSTAR	Integrated System for Trial Allocation and Randomisation
IUGR	intrauterine growth restriction
JOGC	Journal of Obstetrics and Gynaecology Canada

JPMC	Jinnah Post Graduate Medical Center
KT	knowledge translation
LGT	Lionsgate Technology
LHS	lady health supervisor
LHW	lady health worker
LMIC	low- and middle-income countries
MAG-CP	Magnesium Sulphate for Fetal Neuroprotection of the Preterm Infant
MBR	Medical Birth Registry
MCHIP	Maternal and Child Health Integrated Program
MCSP	Maternal Child Survival Program
mHealth	mobile health
MICE	multivariate imputation by chained equations
MMR	maternal mortality rate
MMWG	Maternal Morbidity Working Group
MNCAH	World Health Organization Department of Maternal, Newborn, Child and Adolescent Health
MNH	Maternal and Newborn health
MOM	Mapping Outcomes for Mothers
MSU	Michigan State University
NICU	neonatal intensive care unit
NZAPEC	New Zealand Action on Pre-eclampsia
OBGYN	Obstetrics and Gynaecology
PCA	Principal Component Analysis
PETRA	Planning Evaluation Training Rehearsal and Analysis
PIERS	Pre-eclampsia Integrated Estimate of RiSk
PIGF	placental growth factor
PLOS	Public Library of Science
POM	PIERS on the Move
PPG	photoplethysmogram
PPH	postpartum haemorrhage
PRECISE	Pregnancy Care Integrating Translational Science Everywhere
PREDO	Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction Study
PrePARE	Prematurity Reduction by Pre-eclampsia cARE
PRESEDE	Pregnancy Screening Offers Early Detection of Preclampsia Risk
RCOG	Royal College of Obstetricians & Gynaecologists
RCT	randomized clinical trial
R&D	research & development
REB	research ethics board
SAPS	Simplified Acute Physiology Score
SCC	STRIDER Canada Coordinating Centre
sFlt-1	soluble fms-like tyrosine kinase-1
SOFA	Sequential organ failure assessment score
SOGC	Society of Obstetricians and Gynaecologists of Canada
SpO <sub>2</sub>	Peripheral Capillary Oxygen Saturation
SRI	Sustainable, Responsible, Impact Investing
STRIDER	Sildenafil Therapy In Dismal Prognosis Early-Onset Intrauterine Growth Restriction
SQI	signal quality indices
TAG	Technical Advisory Group
TPR	The Preeclampsia Registry
UCT	University of Cape Town
UNDP	United Nations Development Programme
UNFPA	United Nations Population Fund
UNICAMP	University of Campinas
UNICEF	United Nations International Children's Emergency Fund
UNIFESP	Universidade Federal de São Paulo
US	University of Stellenbosch
USAID	United States Agency for International Development
WAHO	West African Health Organisation
WHO	World Health Organization
WHODAS	World Health Organization Disability Assessment Schedule



ABOVE: Peter von Dadelszen attends a community meeting in the CLIP Pakistan Trial with PI Rahat Qureshi and co-ordinator Zahra Hoodbhoy.

# Introduction & Overview

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## A Year of Transitions

**Welcome to the 2016–2017 PRE-EMPT Annual Report. This seventh annual report provides a summary of the project goals, activities, milestones, and plans within the PRE-EMPT initiative, with a specific focus on activities since November 2016 and plans for the next eight months, at which time our current funding from the Bill & Melinda Gates Foundation will end.**

I want to begin this introduction to the report with a wholly inadequate expression of my personal gratitude to the global PRE-EMPT team. While this report is short on results that we can report, please be sure that we have achieved much and that the impact of our work matters wherever women are most vulnerable to the maternal and perinatal risks associated with pregnancy hypertension and the placental disorders of pregnancy. My own growth as a scientist, obstetrician, feminist and man has been as profound as the distinct change in my hair colour since October 2010!

Approximately 90,000 pre-pregnant and pregnant women have been involved in PRE-EMPT-funded and -related clinical projects during the past seven years, ranging from epidemiology to clinical trials. In addition, the CoLab and Preeclampsia Foundation have access to samples and data from many thousands more women to inform accelerated discovery. Unfortunately, we have enumerated hundreds of maternal, and thousands of perinatal and late neonatal, deaths over that same period.

In the Calcium And Pre-eclampsia Trial (Objective 1), Justus Hofmeyr and the CAP team have implemented strategies to identify and recruit 1,354 women between pregnancies, following a pregnancy complicated by pre-eclampsia. Irrespective of the results of the CAP Trial in terms of prevention of pre-eclampsia, this achievement in implementation itself is singular and worthy of both applause and replication. This replication will be important for future clinical trials but, even more so, for focussed clinical interventions as pre-eclampsia is a gateway condition that identifies future risks for both women and their infants. The numerous ancillary studies described in the CAP report emphasise what can be done when science is adequately funded with a vision of learning beyond the immediate question and maintaining a pipeline of discovery for future innovations that can be implemented at scale. We await the CAP Trial results presentation at the annual meeting in London with barely-disguised impatience.

For Objective 2, Monitoring, much was achieved in developing and validating the miniPIERS model during the first year of PRE-EMPT. miniPIERS and the CRADLE BP device have underwritten the PIERS on the Move (POM) app; the impact of which we are beginning to understand as we analyse each of the Mozambique, Pakistan and India CLIP Trial results. The stories related by APEs, LHWs and ASHAs in each country, respectively, and by those who interact with them, have clearly annotated the utility of well-designed and robustly-supported mHealth-guided care, and the ability of community-based health workers to be better integrated into health systems. This process of mHealth development and implementation at scale has been a major success and speaks to the quality of the teamwork developed within the central and national teams, as well as in-country.

In this year's report, we emphasise recent work in partnership with the CHAI Mozambique team in assessing the performance, and then implementation, of maternal plasma placental growth factor measurement for the assessment of hypertensive pregnant women attending primary health centres in Maputo. In my opinion, of particular importance is the ability of PIGF to identify fetuses at particular risk of stillbirth.

As with the CAP Trial, we are awaiting the results of the Gynuity Health Projects Oral Antihypertensive Trial and the three CLIP Trials with baited breath – all will be presented, as at least preliminary analyses, during the annual meeting. These four tours de force are of major importance. Implementing a change in practice to have colleagues administer and trust three oral antihypertensive agents, even within the context of a clinical trial, is, in itself, an important result of the trial. In settings where colleagues are used to administering parenteral antihypertensives for severe hypertension, learning to trust oral formulations and waiting for them to work is not easy to achieve. Knowing how this was done will be very important as the differential efficacy of nifedipine, labetalol and methyldopa in the management of severe pregnancy hypertension is determined.

The three CLIP Trials, and the parallel implementation project in Nigeria, have entailed the design and implementation of a complex intervention at scale in women's homes and communities. Ministries of Health and Community Health, and their related programmes, have been fully engaged from the design phase, and their unstinting support cannot be acknowledged sufficiently. However, those I most want to thank are the UBC team for their diligence, competence and calm and the national CLIP teams as they worked tirelessly towards the shared goal of improved health outcomes. Zulfi and Laura have been phenomenal co-PIs for CLIP, and Esperança, Khátia, Charfudin, Rahat, Bellad, Ashalata and Shiva have been inspirational national PIs and co-PIs. I have learnt far more than I have taught. I may even know something about cluster RCTs at this point! Currently, we are deep in the analyses of these trials and look forward to sharing our findings at the annual meeting and, subsequently, with the global maternal and perinatal health community.

Having designed and implemented global standards for discovery science related to pregnancy hypertension and placental disorders, the CoLab (Objective 4) has continued to strengthen its less-developed country focus over the past 12 months. The COLLECT database is operational. The Brazilian PrePARE stepped-wedge implementation trial is underway. The PRECISE Network has been funded so that we can better understand pathways to pregnancy complications within the cultural, dietary, and both infectious and chronic disease totality of women's lives. Biological samples from CAP are being analysed. I have to thank Jim and Chris in particular, both of whom, as senior investigators, introduced me to a career in pre-eclampsia science more years ago than any of us would care to admit. Their energy and commitment to CoLab has been beyond admirable – and they've clearly enjoyed themselves.

Knowledge translation and advocacy (Objective 5) within PRE-EMPT began with the 2011 WHO pre-eclampsia recommendations. PrePARE is implementing these recommendations in health centres supporting women in Brazilian favelas in a monitored fashion within the stepped-wedge trial design. In this year's report, we describe the remarkable success of the MAG-CP project in Canada, implementing the use of magnesium sulphate for fetal neuroprotection. With accurate pregnancy dating (e.g., TraCer), understanding how to implement MgSO<sub>4</sub> for this indication will be important for the global maternal and perinatal health community, especially in less-resourced settings where cerebral palsy has particularly devastating consequences for affected infants, their families and their communities.

Finally, my round of thanks. As Laura and I make our transition from St George's to King's College London, we want to thank Lucilla, Andy, Lucy, Kypros, Jane and everyone else at King's for their welcome and support. Through shared activities, we will continue to work with some special people at St George's. Jerker and Nicole, at the Gates Foundation, have been steadfast in their support and encouragement (recently confirming a further supplement to complete specific tasks that will inform implementation of PRE-EMPT's findings). It is a personal delight to share a vision of the future and begin to see how we might get there. While completing her PhD (hooray), Marianne Vidler has proven herself to be an exemplary, cheerful, calm and effective PRE-EMPT manager – our weekly calls are a highlight of my week. I can't thank you and the rest of the Vancouver team enough, Marianne.

France Donnay has remained deeply engaged with PRE-EMPT as we process what has been achieved and envision its future. Since the first day of the PRE-EMPT journey, I have valued her advice and sagacity, tempered with humour and Belgian directness. Thank you.

Finally, I have to thank Laura, her mother, Sheila, and our children. This has been an interesting year at many levels, but the continued love and support of Sheila, Emma, Piers and Will, as well as Eddie and Tess in New Zealand, as they tell their own stories and achieve in their own rights (national team memberships in fencing [Emma] and rugby [Piers], and clothing label [Eddie]) is priceless. We travel, we work long hours and we talk shop, but they support what we do and appear to derive pride from it. Most of all, I thank Laura who is my partner in everything and of whom I am so very, very proud, especially as she takes up her presidency of the International Society for the Study of Hypertension in Pregnancy in October. I know just how lucky I am to have you.

Kind regards,

A handwritten signature in red ink, appearing to read 'Peter von Dadelszen', with a long horizontal line extending to the right.

Peter von Dadelszen



ABOVE: Calcium and Pre-eclampsia PI Justus Hofmeyr reviews patient files with the study team.

# Objective



# Prevention

# The CAP (Calcium And Pre-eclampsia) Trial: a WHO Collaboration

**Principal Investigator:** Justus Hofmeyr

**Trainee (and co-ordinator):** Mandisa Singata

**Funding:** Bill & Melinda Gates Foundation, World Health Organization

## Overview

Epidemiological evidence suggests an association between pre-eclampsia and low dietary calcium. Calcium supplementation in the second half of pregnancy reduces the severe consequences of pre-eclampsia with a trend to reduced deaths as well, but does not reduce pre-eclampsia to the extent expected from the epidemiological data.

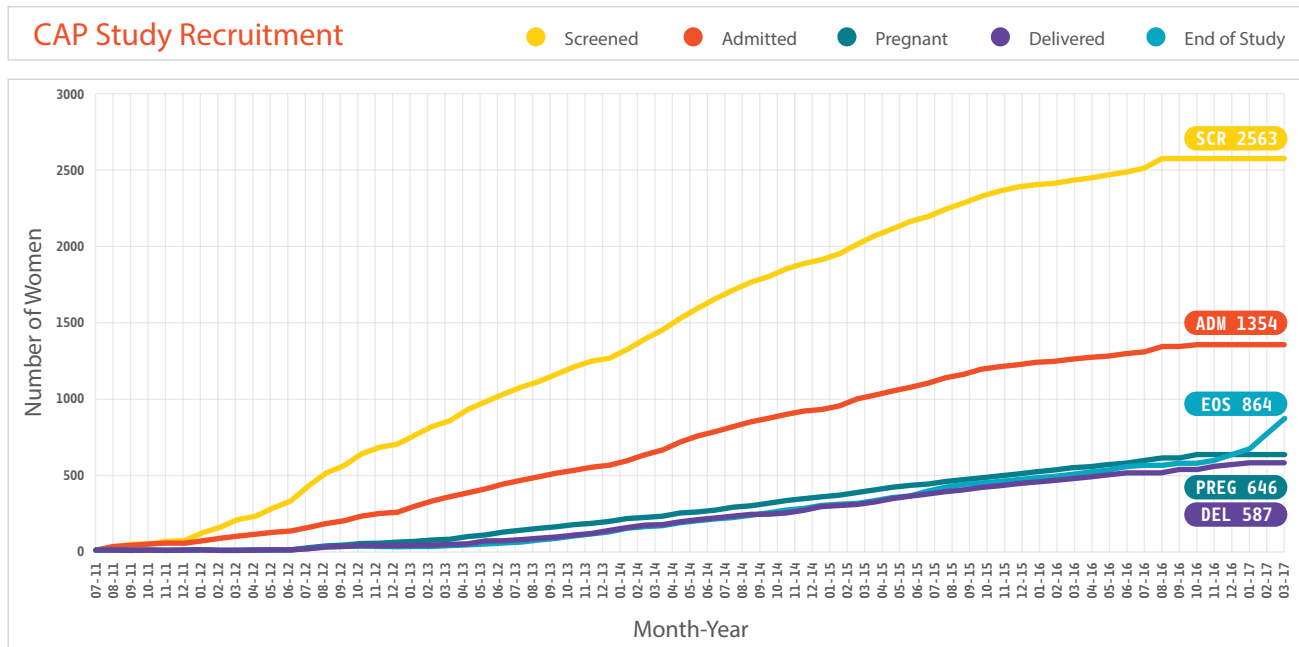
The purpose of the Calcium And Pre-eclampsia (CAP) Trial is to determine whether calcium supplementation before and in early pregnancy reduces pre-eclampsia. This includes the time period when the placental origins of pre-eclampsia are thought to evolve.

Women with a history of pre-eclampsia in their most recent pregnancy, who agree to participate, receive

calcium 500mg daily or placebo from enrolment until they become pregnant, and up to 20 weeks of pregnancy. After 20 weeks all women receive calcium supplementation with 1,500mg daily according to WHO guidelines. The primary outcome is pre-eclampsia. About 1,350 women will be enrolled to achieve the sample size of 540 women contributing data to the primary outcome.

Sub-studies include:

- The effect of calcium supplementation on blood pressure in non-pregnant women with previous pre-eclampsia
- The effect of calcium supplementation on conception
- The effect of calcium supplementation on miscarriage



- The effect of calcium supplementation on urinary calcium creatinine ratio during pregnancy (Sarah Manyame and Jim Roberts)
- Dietary surveys (Gabriela Cormick)
- Pre-eclampsia biomarker study (GSK)

Recruitment commenced at three sites in South Africa and one in Zimbabwe between July 2011 and Feb 2012, and six in Argentina between March 2013 and July 2014.

## Year 7 Progress

During Year 7 we will complete all 3 deliverables listed in our Year 6 report:

- 1 Complete follow-up for our sample size of 540 women with data on pre-eclampsia
- 2 Have final data for the PRE-EMPT meeting in London, October 2017
- 3 Complete 2-3 additional ancillary publications

Recruitment as of the end of July 2017:

- 1,354 women recruited (64 since Year 6 report)
- 650 women pregnant (73 since Year 6 report)
- 633 women delivered (133 since Year 6 report)

Of 633 completed pregnancies, 81 ended in miscarriage.

We have thus achieved our sample size of 540 women with completed pregnancies which progressed to 20 weeks or more. This should enable us to discuss the final results at the PRE-EMPT meeting in October.

## Agreement with the CISMAC Consortium

In Year 7, we approached the Centre for Intervention Science in Maternal and Child Health (CISMAC) for additional funding for the CAP Trial. CISMAC supports research aiming to improve health and survival of mothers and children as well as child development in low-income populations in Asia and Sub-Saharan Africa.

CISMAC agreed to provide financial support to CAP for the statistical analysis of the trial in 2017 as well as the writing of two scientific manuscripts:

- 1 Recruitment and retention in longitudinal pre-conception randomized trials: challenges and lessons learnt from the CAP Trial. This paper describes the methods for pre-pregnancy recruitment and retention, as well as challenges and barriers encountered (Submitted).
- 2 “Calcium dietary intake assessment in women in South Africa and Zimbabwe participating in the CAP randomized controlled trial.” This analysis and corresponding manuscript aims to estimate mean daily calcium intake of women participating in the CAP Study during their second trimester of pregnancy; within-person variability using a repeated dietary assessment in a sub sample of pregnant women; and the proportion of women participating in the CAP Study with intakes below requirements of 800 mg of calcium per day.

The first manuscript is led by Tess Lawrie and the second by the Gabriela Cormick.

In addition, the agreement includes an educational and training component. Armando Seuc will work and supervise young statisticians from CISMAC who can eventually contribute and help with future secondary analyses of the CAP Trial.

## Ideal Interpregnancy Interval for Women with Pre-eclampsia

One of the issues faced during recruitment for the CAP Study was the controversial question regarding the ideal interpregnancy interval following a pregnancy complicated by pre-eclampsia. Some authorities recommend an extended interpregnancy interval to reduce the risk of recurrent pre-eclampsia. On the other hand, many prospective participants who had lost a pregnancy due to severe pre-eclampsia/eclampsia were anxious to conceive as soon as possible. One of the activities of the CAP study group has been a systematic review of interpregnancy interval and risk of recurrent pre-eclampsia, led by Gabriela Cormick (see publications below). Following a systematic search, four cohort studies were included. No evidence was found that interpregnancy intervals of less than two years were associated

with increased risk of recurrent pre-eclampsia. With intervals of greater than four years, the risk appeared to increase. These data need to be interpreted cautiously as they are based on observational studies that are inherently subject to confounding.

## A Tale of Two Cities

In February 2012, one participant from Cecilia Makiwane Hospital in East London moved to Johannesburg and was transferred to Chris Hani Baragwanath Hospital for follow-up. While living in Johannesburg, she became pregnant. However, her husband was transferred back to East London so she was re-transferred to the CAP site at Cecilia Makiwane where she gave birth a healthy daughter in 2013.

Catherine moved to East London this year, based mainly at Frere Hospital. One day, she was helping out at Cecilia Makiwane Hospital and happened to bump into the participant. The participant was looking for the CAP study office to thank us for her healthy 3 year old and to ask if she could join the trial again as she was ready for another child! The family gave permission for us to show their photograph.

This study illustrates the positive impact the CAP Trial and the dedicated staff had on families and the communities.

## Discontinuation of Non-pregnant Participants

A novel feature of the CAP Study has been the need to discontinue participants who have not become pregnant in an ethical way. To appropriately address the discontinuation of these participants, guidance to the study staff and a letter to participants were developed.

*Our thanks to Ana Pilar Betran for researching and putting together a carefully considered process.*

### Steps to Discontinue Non-pregnant Women

- Discontinue the women in a face-to-face interview. Ideally, each participant could be discontinued in her next PPV appointment. Do not resupply tablets in the discontinuation visit.



- Print the explanatory letter (translated into local languages if necessary) to be given to the woman so she can take it home.
- Do a pregnancy test to make sure that she is not pregnant. If the test is negative, proceed to discontinue the participant. If the test is positive, continue the women in the study as per standard procedures of the trial.
- Explain that the trial has finished and that she will no longer need to come for the trial visits and that she will no longer receive the tablets that she received since she entered the trial.
- Explain that we are giving her an explanatory letter to take home and read and she can give the letter to her regular healthcare provider.
- Explain that she should continue her regular health care with her healthcare provider as she was doing during the study.

- If you think it is appropriate and possible, you may ask her if she would like you to schedule an appointment with a fertility clinic.
- Explain that we will call her in 6 weeks to check on her health as we have been doing during the study (the inter-visits phone calls).
- If the woman asks about continuing supplementation (e.g. buying calcium or other supplements in the pharmacy), ask her to contact her regular healthcare provider and discuss with him/her.
- Ask her if she wants the study finding to be communicated to her and if so, how we should do this (e.g. letter, email, telephone).
- If the participants shows interest in knowing if they have been in the intervention arm or a control arm of the study, explain that breaking the code at this moment is not possible. Later on when the summary results are available, this information could be made available to individual participants if they request it.
- Allow participants to ask you in person any questions they may have.

### Discontinuation Letter to Participants

*Dear CAP study Participant,*

*This letter is to tell you that the CAP Study is drawing to a close. In this study you were randomly allocated (i.e. like spinning a coin) to tablets with calcium or to similar tablets but without calcium. Neither you nor we know which treatment you are receiving during your participation in the study. Our objective was to measure the effect of calcium on blood pressure and health, and the health and growth of the baby of those women who fell pregnant during the study period.*

*Closure of the trial means that you will no longer need to come for the trial visits and you will no longer receive the tablets that you have had since you entered the trial. You should now continue your regular health care with your healthcare provider as you were also doing during the study. Please, share this letter with your healthcare provider. You should also continue your regular life without concern for not continuing the tablets. We will call you in six weeks to check on your health.*

*We expect to have the summary findings of the study near the end of 2017. If you wish to know the results, please let us know how you would like us to tell you about them: by a letter, email or telephone call.*

*We would like to thank you for your participation, time and interest on this CAP Study. Your participation has been an important contribution to advance research and improve healthcare of pregnant women in the future.*

*Sincerely yours,*

*Principal Investigator*

### Urine Studies

The RCOG 2017 conference in Cape Town (20-22 March 2017) provided the opportunity for Stephen Munjanja, Sarah Manyame, Jim Roberts and Justus Hofmeyr to meet and discuss the urine biochemical studies of the calcium/creatinine ratio and protein creatinine ratio, which were planned as part of this study. The analysis of Zimbabwean samples will be done by Sarah in Harare, and the rest by the University of Stellenbosch biobank facility in Tygerberg, Cape Town. The studies will be complemented by a case control study of urinary predictors of pre-eclampsia done in Harare, which will be the basis of Sarah's PhD. Sarah and Jim met with Carmen Swanepoel of Stellenbosch University to discuss using other CAP's urines as a validation group in a collaboration between Sarah and Carmen.

### Data Analysis Plan

The unique strategy of recruiting women prior to pregnancy raises several interesting methodological issues regarding analysis. In particular, intermediate outcomes on the causal pathway between the intervention and the primary outcome need to be taken into account. Armando Seuc, the trial's statistician, is an expert who has published in the field.

Thanks to Armando Seuc for tackling the complexity of this study in terms of intermediate outcomes:

- 1 They do not prevent us from observing the main outcome.
- 2 They prevent us from observing the main outcome, but the main outcome does exist and can be imputed.
  - For example, loss-to-follow-up.
- 3 They prevent us from observing the main outcome, and the main outcome is not defined for some categories of the intermediate outcome.
  - For example, pregnancy and early pregnancy loss (before 20 weeks' gestation).

The first two are common and will be dealt with following standard protocols.

In the third scenario, if pregnancy and early pregnancy loss are independent of calcium assignment (similar between groups), we will be able to do a simple binomial comparison of women with pre-eclampsia who have a pregnancy beyond 20 weeks in each group. If pregnancy and/or early pregnancy loss is not independent of the assignment, we will include compound outcomes 'pre-eclampsia or early pregnancy loss, or 'pre-eclampsia or no pregnancy', as indicated. In addition, we will apply survival analysis with competing risks to complement the results using the binomial rates approach as this technique is well equipped to handle the sequence of intermediate outcomes.

## Archiving of Biomarker Study Biological Samples

The CAP Study team and CoLab collaborated with GSK Maternal and Neonatal Health Unit, Global Health R&D Unit, R&D Alternative Discovery & Development, who measured a comprehensive panel of putative pre-eclampsia biomarkers on a sub-set of the CAP Study population. The laboratory analyses in the UK are complete. Originally, excess samples were to be stored in the US but we now have the capacity for long-term archiving of the samples at the University of Stellenbosche biobank in South Africa.



Arrangements are currently being put in place to do this and the samples will be available for future pre-eclampsia research.

## Year 8 Deliverables

During Year 8, we plan to publish the main trial findings as well as several sub-study reports, and to complete the laboratory studies. If the study shows clinically meaningful benefit from calcium supplementation, we plan to embark on strategies to implement the findings.

## Publications

- Hofmeyr GJ on behalf of the CAP study group. The role of calcium in hypertension and pre-eclampsia. Cape Town cardiac disease in Pregnancy symposium, Hatter Institute for cardiovascular Research in Africa, 28/09/2016.



ABOVE: The Calcium and Pre-eclampsia team present at the PRE-EMPT Annual Meeting in Seattle, 2014.



ABOVE: The Microlife CRADLE Vital Signs Alert, a modified version of the CRADLE blood pressure device, which measures blood pressure and heart rate and incorporates a traffic light early warning system.

Objective



Monitoring

# Objective 2: Monitoring Timeline

## miniPIERS

- SEP 01 2007 — CIHR funding secured to initiate LMIC cohort
- AUG 01 2010 — WHO funding secured to expand LMIC cohort
- Sites Activated**
- JUN 01 2008 — South Africa
- JUN 19 2008 — Fiji
- AUG 13 2008 — Uganda
- JUL 14 2009 — Pakistan
- MAR 16 2011 — China
- JUN 17 2011 — Brazil
  
- MAR 30 2012 — Recruitment complete
- JAN 21 2014 — Model developed, validated and published



## CRADLE

- JAN 01 2015 — CRADLE 2 Study starts
- MAY 01 2015 — CRADLE is nominated as one of the top 30 innovations that could accelerate progress towards the SDGs (PATH Innovation Countdown 2030)



- APR 01 2016 — CRADLE 3 Study starts
- MAY 01 2017 — CRADLE 2 Study is complete
- MAY 01 2017 — CRADLE is shortlisted for the PLIS Alliance prize for innovation
- DEC 01 2017 — CRADLE 3 Study is complete



## Maternal Morbidity Working Group

- FEB 01 2014** — Meeting is held in Istanbul to determine the health conditions attributed to and/or complicating pregnancy and childbirth that have a negative impact on wellbeing and/or functioning
- FEB 01 2017** — Stakeholder meeting is held in Geneva

## Pulse Oximetry

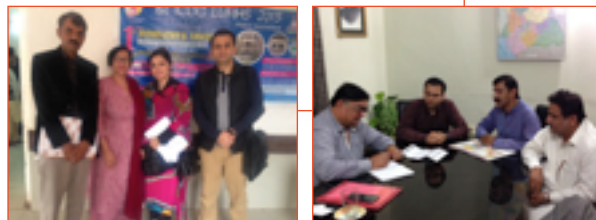
- MAR 31 2012** — Pulse oximetry with miniPIERS data collection ends in Pakistan
- DEC 31 2013** — Pulse oximetry with miniPIERS data collection ends in South Africa
- JAN 18 2015** — Pulse oximetry is introduced in the CLIP Pakistan Trial
- FEB 24 2015** — Pulse oximetry is introduced in the CLIP Mozambique Trial
- AUG 01 2015** — Pulse oximetry waveform morphology analysis begins

## PIERS on the Move

- OCT 25 2011** — Funding received from GCC for POM development
- AUG 01 2013** — Clinical validation study recruitment complete
- APR 05 2015** — Usability studies end in South Africa
- DEC 15 2016** — Clinical cohort complete for hypotension prediction model

## Economic analysis of the CLIP Trials

- NOV 01 2014** — Data collectors in Pakistan receive training
- JAN 01 2015** — Data collection begins in Pakistan



- MAY 01 2015** — Publication of the study protocol
- FEB 01 2016** — Site visit (Pakistan): Health facility costs
- JUN 01 2017** — Manuscript on the societal cost drivers in Pakistan is published



# miniPIERS (Pre-eclampsia Integrated Estimate of RiSk)

**Principal Investigator:** Peter von Dadelszen

**Trainee (and co-ordinator):** Beth Payne (Post-doctoral fellow)

**Funding:** Bill & Melinda Gates Foundation, Canadian Institutes of Health Research, World Health Organization, Preeclampsia Foundation, Rockefeller Foundation, International Federation of Gynecology and Obstetrics

## Overview

The hypertensive disorders of pregnancy (HDP) are one of the leading causes of maternal death and morbidity in low-resourced countries, due to delays in case identification and a shortage of health workers trained to manage these disorders. The objective of the miniPIERS study was to develop an evidence-based tool that can aid in decision making around the care of women with HDP.

From 1 July 2008 to 31 March 2012, in five low- and middle-income countries (LMIC), data were collected prospectively on 2081 women with any hypertensive disorder of pregnancy admitted to a participating centre. Candidate predictors collected within 24 hours of admission were entered into a step-wise backward elimination logistic regression model to predict a composite adverse maternal outcome within 48 hours of admission. Model internal validation was accomplished by bootstrapping and external validation was completed using data from 1300 women in the fullPIERS dataset. Predictive performance was assessed for calibration, discrimination, and stratification capacity.

The final miniPIERS model included: parity (nulliparous vs. multiparous); gestational age on admission; headache/visual disturbances; chest pain/ dyspnoea; vaginal bleeding with abdominal pain; systolic blood pressure; and dipstick proteinuria. This model was well-calibrated and had an area under the receiver operating characteristic curve (AUC ROC) of 0.768 (95% CI 0.735 - 0.801) with an average optimism of 0.037. External validation AUC ROC was 0.713 (95% CI 0.658 - 0.768). A predicted probability  $\geq 25\%$  to define a positive test classified women with 85.5% accuracy. Limitations of this study include the composite outcome and the broad inclusion criteria of any hypertensive disorder of pregnancy. This broad approach was used to optimize model generalizability.

The miniPIERS model can identify women at increased risk of adverse maternal outcomes associated with the hypertensive disorders of pregnancy. It can be used in LMICs to identify women who would benefit most from interventions such as MgSO<sub>4</sub>, antihypertensives, or transportation to a higher level of care.

## Year 7 Progress

The miniPIERS project concluded its active phase of research in 2012. Data from this study continue to be a rich source of knowledge generation for the wider PRE-EMPT collaborative group with two additional publications being generated using these data this year.

## Year 8 Deliverables

Our goal is to develop methodology for updating the prediction model after clinical implementation and to use these new methods to update the miniPIERS model as needed. This will be possible once data from the CLIP trials are released for secondary analysis in 2018.

## Publications

- Payne B, Groen H, Platt R, von Dadelszen P, Hutcheon JA (2017) Understanding sources of overfitting in clinical prediction models: the contributions of variable coding, variable selection and parameter estimation. *Med Decis Making*. (submitted 05/2017)
- Ukah UV, Payne B, Lee T, Magee LA, von Dadelszen P. External validation of the fullPIERS model for predicting adverse maternal outcomes in pregnancy hypertension in low-and middle-income countries. *Hypertension*. 2017;69:705-711

# Community Blood Pressure Monitoring in Rural Africa and Asia: the Detection of Underlying Pre-eclampsia and Shock (CRADLE)

**Principal Investigator:** Andrew Shennan

**Trainee and Co-ordinator:** Hannah Nathan

**Collaborators:** Annemarie de Greeff (South Africa), Wilhelm Steyn (South Africa), John Anthony (South Africa), Suellen Miller (USA), Gerhard Frick (Microlife™)

**Funding:** Bill & Melinda Gates Foundation

## Overview

Accurate and regular blood pressure (BP) monitoring is a cost-effective screening tool for the early identification and management of pre-eclampsia. In low- and middle-income countries (LMICs), pre-eclampsia is frequently under-detected because there is low attendance for antenatal care, inadequate training in how to take accurate BP measurements, and insufficient, poorly functioning equipment. Moreover, training for the use of the traditional sphygmomanometer, an inexpensive yet technically challenging method, is often lacking amongst health care workers in antenatal clinics. Additionally, there is concern over the robustness and safety of these traditional devices that contain mercury. Furthermore, the next generation aneroid instruments are frequently inaccurate through calibration drift and ideally require six-monthly re-calibration to maintain accuracy. Lastly, the use of 'manual' BP devices, which require auscultatory skills and the observer recording the BP from a calibrated scale, is associated with user-bias resulting in inaccurate measurement. Third-generation BP devices that automatically inflate and provide a digital reading, while circumventing some of these issues, are also unsuited for use in LMICs as they depend on an expensive power supply to drive the automatic pump or batteries, which have poor resistance to shock and fluctuations in temperature. Therefore, most BP devices are inaccurate and underestimate the BP in hypertensive pregnancies. Accurate BP measurement is not only vital for detecting and monitoring pre-eclampsia and other hypertensive disorders of pregnancy, but also other life threatening

maternal conditions such as postpartum haemorrhage (PPH), as well as intrapartum and antepartum haemorrhage, and sepsis. PPH, sepsis and pre-eclampsia are the leading direct causes of maternal death and morbidity in LMICs. Early recognition is essential given that PPH can lead to death within two hours. However, visual estimation of blood loss is often unreliable, as is the relationship of blood loss to maternal symptoms. Hypovolaemic shock may be complicated by anaemia, resulting in a greater degree of compromise related to blood loss. Furthermore, blood loss may be concealed (e.g. placental abruption). An early community diagnosis rather than waiting until the woman is symptomatic, or until the blood loss reaches a defined level, would quickly alert the community health care provider to severe maternal compromise, potentially prompt appropriate community-based initiation of treatment of the patient (e.g. intravenous fluids and antibiotics) and/or emergency transfer for definitive care.

## The CRADLE Project

The King's College London CRADLE research group, in collaboration with Microlife, has developed a semi-automated BP device (Microlife 3AS1-2, modified: Microlife CRADLE Vital Signs Alert (VSA)) specifically for use in LMICs.

The CRADLE group has clinically validated this device for use in pregnancy (including pre-eclampsia) and in pregnant women with low blood pressure. This is the first validation of an automated BP device at low blood

pressures. The device comprises of a micro-USB port and a sealed rechargeable lithium battery pack, allowing charging through generic mobile phone chargers. The manual inflation function allows for long battery life. Despite its accuracy and suitability for low-resource settings, the device remains less than \$20 per unit.

A traffic-light early warning system within the device alerts users to abnormalities in blood pressure (hypertensive disorders in pregnancy and shock secondary to haemorrhage and sepsis). The traffic light display was determined through qualitative evaluation of a number of display options. Predefined blood pressure thresholds, used as hypertension triggers for the CLIP Trials have been incorporated into the device's traffic light system. For shock triggers, the CRADLE group retrospectively analysed datasets of women with PPH. There was one dataset in the UK and another large dataset of women in four African low-resource settings, in collaboration with Suellen Miller and the Safe Motherhood Program, University of California, San Francisco. The optimal vital signs predictor of adverse clinical outcomes was determined: Shock Index (the ratio of pulse to systolic BP). Two Shock Index thresholds were determined according to the increased risk of adverse outcome, and introduced as the amber and red shock triggers within the traffic light system.

The Microlife CRADLE VSA device was nominated by independent experts from more than 500 innovations, from over fifty countries around the world, as one of thirty high impact innovations to save lives to be a leading innovation in the maternal, child, and newborn category. As part of Reimagining Global Health,

from the inaugural report of the Innovation Countdown 2030 initiative.

To date the CRADLE VSA has been implemented clinically into over twelve countries in Africa, Asia and the Caribbean (n=6700 devices), sometimes being the first BP device available to a clinic and in most cases, the first accurate BP device in clinics and hospitals.

*“Yes Sir ... Anyone can learn using this device. If we check their BP ... even they themselves can know how much is their BP. If they are well educated they themselves can know their BP reading by seeing at the device display. If they go to hospital the hospital people will simply say that, their BP is normal or not. Now at the same time when we are checking their BP the people nearby us can also see the number and they can also understand this ... even anyone in the family can also come to know about this.”*

—Accredited Social Health Activist (ASHA) worker in Karnataka, India

*“I feel happy about it. After we have started checking the BP even people have started respecting us more. They are also happy about it.”*

—Accredited Social Health Activist (ASHA) worker in Karnataka, India

## Year 7 Progress

In 2015-16, we completed a 15-month clinical evaluation of the Microlife CRADLE VSA device in the maternity departments of three large South African hospitals (Groote Schuur, Tygerberg, and Kimberley) to prospectively evaluate the predictive ability of the hypertension and shock thresholds within the device's traffic light early warning system. Over the last few months, we have been cleaning and analysing data from 1547 women with pre-eclampsia, 283 women with obstetric haemorrhage and 126 women with maternal sepsis. As well as validating the traffic light early warning system thresholds, our work demonstrated the high incidence of complications of pre-eclampsia, haemorrhage and sepsis in these cohorts. This work will be included in three manuscripts which will be submitted for publication during the summer of 2017.

The qualitative evaluation of the acceptability, usability and feasibility of the device with a range of facility-level healthcare providers is now complete. We interviewed 158 participants and

convened six focus group discussions with healthcare providers, pregnant women and their families across South Africa, Mozambique, India and Nigeria. The CRADLE device was well-accepted by healthcare workers from a wide-range of facilities and levels of experience. The traffic

## Stories from the Field

### Viernan's Story of Success

In Haiti, most women deliver at home with traditional birth attendants (*Matwon's*) who, in our trial area are guided by trained volunteers (Agent Sante). One Agent Sante, named Viernan, works in a remote village called Labadee, which is 45 minutes on foot to the nearest passable road. In January 2017, he was trained to use the CRADLE VSA. Three days later, he reported that he had seen two women with red lights in labour that he had referred to the hospital. Both had safely returned. One had had a Caesarean and the other was given tablets to treat hypertension. They reported that their lives and their baby's lives were saved. Viernan stood proudly and told the story to the pregnant women in the village to encourage them to have regular blood pressure readings.

lights early warning system was unanimously reported positively, giving health care workers confidence with decision-making and a sense of professionalism. This work will be submitted for publication in the next few weeks.

CRADLE has provided the BP devices for community-based health care workers at all intervention cluster sites in the CLIP Trials. A total of 695 Microlife 3AS1-2 BP devices have been provided in Mozambique, India, and Pakistan; 293 of the modified CRADLE VSA device (with traffic light early warning system) were used in Nigeria. Quantitative CRADLE-specific outcomes have been collected to evaluate the impact of the introduction of the device on routine antenatal care, diagnosis of pre-eclampsia and rates of adverse clinical outcomes. Data cleaning has begun and the analysis will take place over the summer of 2017.

The CRADLE 3 Trial (funded by Medical Research Council (UK), Department of Biotechnology (India), Department for International Development (UK)) is a multi-centre stepped-wedge randomised control trial introducing the CRADLE VSA device and an educational package into routine maternity care in low-income settings to determine whether it can reduce the number of women that have severe pregnancy complications. The trial commenced in March 2016 in ten low-income settings (India, Zimbabwe, Zambia, Sierra Leone, Uganda, Malawi and Haiti) and will run for twenty-one months. We have now successfully implemented the CRADLE 3 package

into 8 of the 10 centres. This has included distribution of over 3000 CRADLE VSA and trained over 1500 health care professionals. Alongside the main trial outcomes we are also evaluating the way that the trial is delivered and how it may interact in different contexts.

### Year 8 Deliverables

Renal impairment was common in our cohort of women with pre-eclampsia in South Africa. Considering the impact acute kidney injury can have on long-term outcomes for women with pre-eclampsia, we are collecting more data on those women with renal impairment to explore their renal profile during their admission and their clinical care following discharge from hospital.

For CRADLE 3, the last site will implement in early October 2017 and data collection will complete by January 2018. We hope to disseminate results by autumn 2018.

We look forward to presenting and disseminating the CRADLE 2 output in 2017 and early 2018.

### Publications

- Nathan HL, Cottam K, Hezelgrave NL, Seed PT, Briley A, Bewley S, Chappell LC, Shennan AH. Determination of normal ranges of shock index and other haemodynamic variables in the immediate postpartum period: a cohort study. *PLoS One*. 2016;11(12)

# Maternal Mortality and Maternal Morbidity (in Conjunction with the WHO Maternal Morbidity Working Group)

**Principal Investigator:** Lale Say

**Co-ordinator:** Doris Chou

**Funding:** Bill & Melinda Gates Foundation, World Health Organization

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## Overview

PRE-EMPT members Peter von Dadelszen, Tabassum Firoz and Laura Magee continue to participate in the WHO Maternal Morbidity Working Group (MMWG). This four-year project concluded earlier this year with a broader meeting with stakeholders held in February 2017 in Geneva. Of the project's five objectives, the first was achieved in 2014, and the remainder were achieved in 2016-7. Progress on all objectives is summarized below.

## Year 7 Progress

### **Objective #1: Construct a Definition and Develop Identification Criteria for Maternal Morbidity**

Any health condition attributed to and/or complicating pregnancy and childbirth that has a negative impact on the woman's wellbeing and/or functioning. (Istanbul, Turkey, 2014)

### **Objective #2: Estimate the Burden of Individual Causes of Maternal Morbidity Based on Existing Evidence**

Adding to published systematic reviews on sexual dysfunction and myocardial infarction, new reviews on the prevalence of chronic hypertension, sepsis, and peripartum psychosis are in preparation. The MMWG is also in the process of completing a systematic review on the assessment of health-related functioning and a qualitative synthesis of the experience of maternal morbidity.

### **Objective #3: Develop an Assessment Tool for Measuring Maternal Morbidity at the Community and Primary-Health-Care Levels in Low- and Middle-Income Countries**

The MMWG previously developed a matrix of 121 conditions and associated signs, symptoms, investigations and management strategies, and their consequences. The matrix has three dimensions: the conditions, their functional impact, and a thorough maternal history. The matrix was translated to a tool, with both antepartum and postpartum modules.

### **Objective #4: Validate the Assessment Tool in Three Low- and Middle-Income Countries**

The assessment tool was piloted in Jamaica, Kenya, and Malawi to determine the feasibility, acceptability and utility of implementing a modified, streamlined tool for measurement and summary estimates. The pilot study found that conditions with high case-fatality rates were not necessarily those contributing to maternal morbidity, and that the most common medical conditions are not obstetric. It also highlighted the importance of incorporating sexual health into routine history taking in all sites and in Jamaica, the high rate of intimate-partner violence (IPV) and exposure to substance abuse.

The team has since focussed on refining the tool based on the feedback received during the February meeting. Some of these changes included moving mental health into medical morbidities, collapsing categories and using self-reporting instead of physician diagnosis for measuring IPV. Principal Component Analysis (PCA) and decision tree analysis were conducted to analyse symptoms. While the PCA was not useful for revising the tool, the decision tree results were used to identify discriminatory symptoms for

diagnosing hypertensive disorders, thereby increasing the specificity of the tool.

Related to the third and fourth objectives, the MMWG has focussed on functioning as a way to measure and understand morbidity. In addition to the tool, which includes an assessment of functioning, MMWG members from UNICAMP in Brazil completed several analyses validating the 12-item World Health Organization Disability Assessment Schedule (WHODAS 2.0). The tool was validated for screening of functioning and disability associated with pregnancy and history of severe maternal morbidity. The group also looked at the impact of hypertension, haemorrhage and other maternal morbidities on functioning in the postpartum period as assessed by the WHODAS 2.0 tool. Finally, the group sought to establish suggested cut-offs for impaired functionality postpartum using the WHODAS 2.0 tool.

## Year 8 Deliverables

### **Objective #5: Develop Indicators of Maternal Morbidity for Population-Level Tracking**

This objective will be addressed in the next step of the project. Plans are underway to submit a Phase 2 proposal, which will include components related to research, policy, health systems strengthening and education. The group plans to validate the tool that is a scientifically credible, user-friendly, practical and informative. Plans also include developing a screening tool, addressing knowledge gaps and neglected aspects of maternal morbidity and harmonizing a set of core outcomes for maternal morbidity research.

The MMWG plans on publishing a supplement which will include the results of the pilot study, WHODAS studies, systematic reviews and a concluding paper on implementing interventions based on the output of the MMWG.

## Publications

- Gibson P, Narous M, Firoz T, Barreix M, Say L, James L. Incidence of myocardial infarction in pregnancy: a systematic review and meta-analysis of population-based studies. Accepted by Eur Heart J Qual Care Clin Outcomes. (submitted 01/2017)

# Pulse Oximetry

**Principal Investigators:** Mark Ansermino, Guy Dumont and Peter von Dadelszen

**Trainees (co-ordinators):** Dustin Dunsmuir, Beth Payne (Post-doctoral fellow), Bárbara Monserrat Ramos Macías (Masters student)

**Funding:** Bill & Melinda Gates Foundation; Saving Lives at Birth (Grand Challenges Canada)

## Overview

As part of the 'Monitoring' objective of PRE-EMPT, the team has developed a tool called "PIERS (Pre-eclampsia Integrated Estimate of RiSk) on the Move." This tool integrates the miniPIERS adverse outcome prediction model and the Phone Oximeter™ to create a portable, low-cost device that rapidly and reliably identifies women and infants in low- and middle-income countries (LMICs) that are at increased risk of adverse outcomes from the hypertensive disorders of pregnancy. The PIERS on the Move (POM) mobile application was used for assessments of pregnant and postpartum women within the Community-Level Interventions for Pre-eclampsia (CLIP) Trials. In the definitive trials in Pakistan and Mozambique, POM was used to record a photoplethysmography (PPG) signal through a pulse oximetry sensor connected to a tablet. Blood oxygen saturation (SpO<sub>2</sub>) is derived from the PPG and incorporated into the miniPIERS model. A baseline measurement of SpO<sub>2</sub> was done (during the first assessment) and then for any women that were found to be hypertensive ( $\geq 140$  systolic blood pressure). A low SpO<sub>2</sub> ( $\leq 93\%$ ) triggers a recommendation of urgent referral within the application.

Data collection in the CLIP Trial, including pulse oximetry has now finished in all countries. Throughout the CLIP Definitive Trials, we supplied feedback in the form of quality and user progress reports to each country team, and the average quality of recordings continued to improve throughout the trial. These improvements were made by targeted training of users, improvements in the durability of the pulse oximeters, and updating the software to facilitate higher quality recordings.

Currently, we are preparing to analyse the large collection of PPG waveforms along with outcome data to determine if the miniPIERS model could be improved by including features of the waveform morphology.

## Year 7 Progress

Throughout the year, we assessed the quality of the pulse oximetry signals by user and provided feedback to the sites. Every two months, all users were ranked in the report by the number of good quality recordings they recorded and the local teams in Pakistan and Mozambique then identified community health care workers (CHWs) who required additional training. This training continued to improve the average SpO<sub>2</sub> recording quality, which was higher than the year before due to sensor retrofitting (to improve durability) and software updates rejecting low quality recordings.

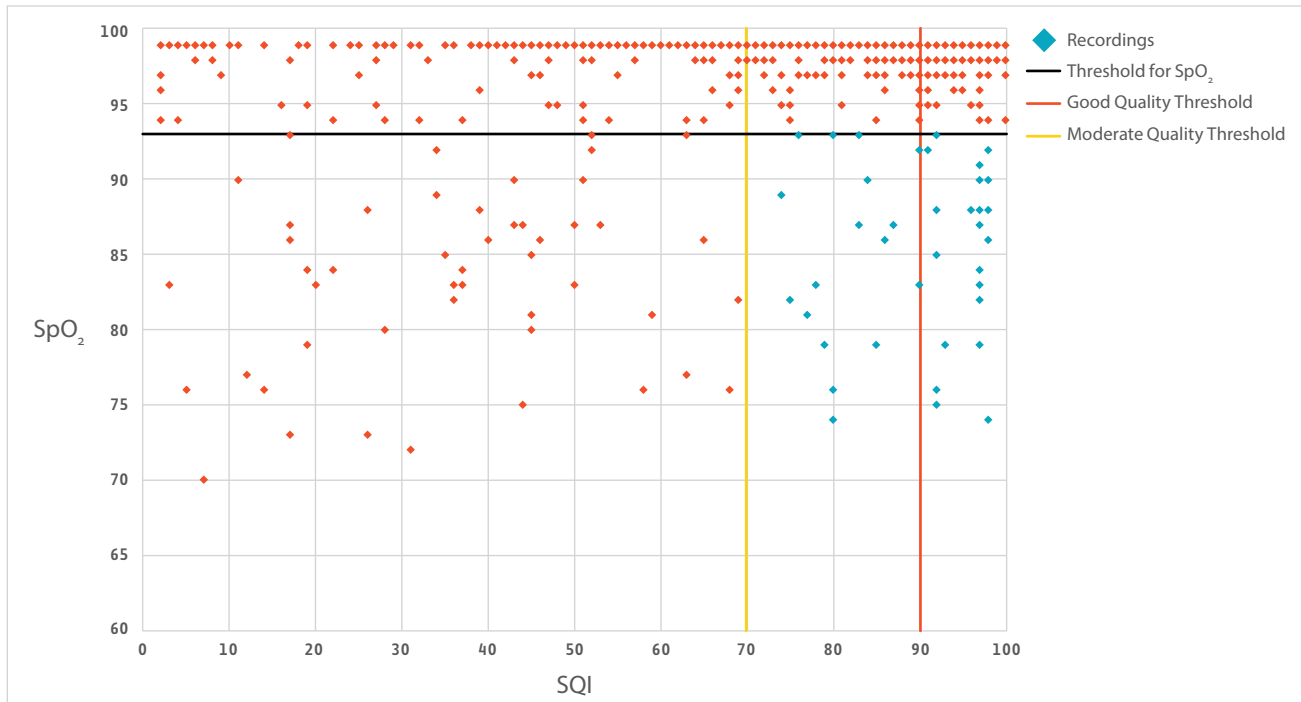
With the CLIP Trial data collection finished, we have collected a total of 10,050 SpO<sub>2</sub> recordings from 215 CHWs in Pakistan and 4,751 SpO<sub>2</sub> recordings from 48 CHWs in Mozambique. The raw PPG waveforms from these recordings were uploaded during synchronisation to REDCap within each country and then transferred along with de-identified data to Vancouver. An ethics application to start the analysis of the PPG waveform features was submitted, and we are ready to begin the analysis once ethics approval is received.

## Year 8 Deliverables

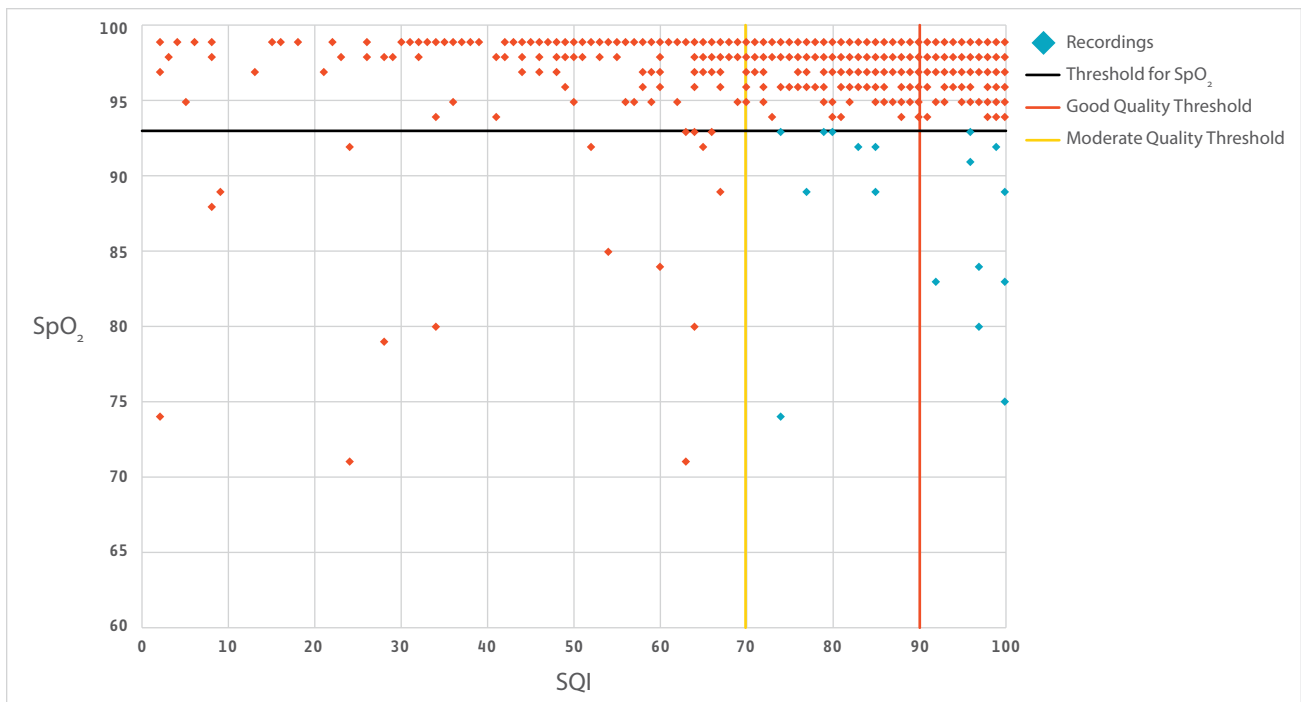
We aim to investigate different signal quality indices (SQIs) to identify the optimal SQI for collecting high quality PPG signals. The POM application SQI algorithm consisted mostly of the Perfusion Index; however, by exploring other indices we may improve the assessment of the signals. Once this is done, future mobile applications can make use of the optimal SQI to improve data collection.

The PPG waveform analyses will be investigated as a method to capture other pre-eclampsia-related symptoms, such as increased arterial stiffness; these could be used to improve the miniPIERS prediction model. By further analysing PPG signals, we may be able to characterise the PPG waveform morphology more thoroughly for pre-eclampsia-related clinical assessments.

### SpO<sub>2</sub> and Signal Quality Index (SQI) in Pakistan



### SpO<sub>2</sub> and Signal Quality Index (SQI) in Mozambique



ABOVE TOP: Scatterplot of SpO<sub>2</sub> and Signal Quality Index (SQI) of recordings in Pakistan.

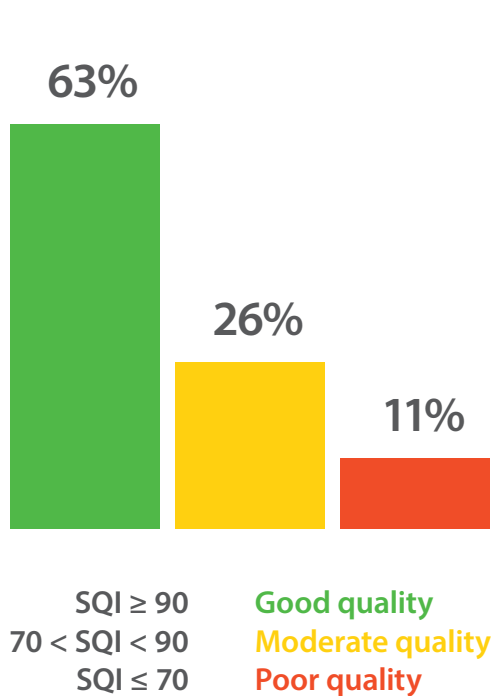
ABOVE BOTTOM: Scatterplot of SpO<sub>2</sub> and Signal Quality Index (SQI) of recordings in Mozambique.

# Mozambique REPORT

**4,751** Recordings  
**48** Users

## Signal Quality Index (SQI)

Below are the recordings broken down into three quality categories

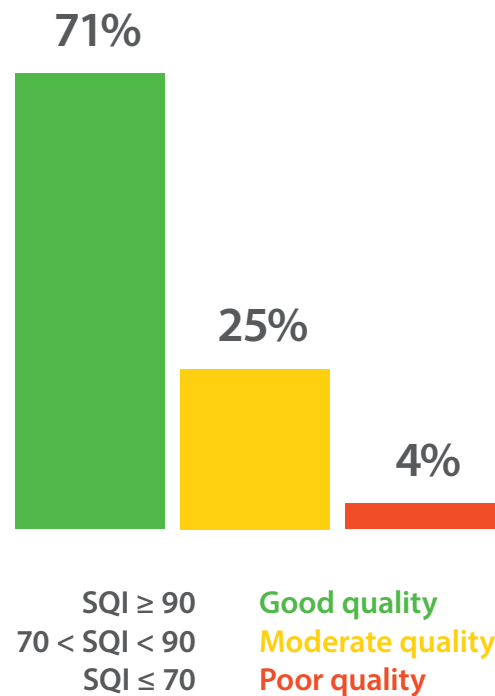


# Pakistan REPORT

**10,050** Recordings  
**215** Users

## Signal Quality Index (SQI)

Below are the recordings broken down into three quality categories



# PIERS on the Move: Transitioning from Pre-eclampsia to Pregnancy and Neonatal Care

**Principal Investigators:** Mark Ansermino and Peter von Dadelszen

**Pakistan Principal Investigators:** Rahat Qureshi, Shereen Bhutta, Sana Sheikh, and Zahra Hoodbhoy

**Trainees (and co-ordinator):** Samina Bakhtawar (Masters student); Beth Payne (Post-doctoral fellow)

**Funding:** Saving Lives at Birth (Grand Challenges Canada)

## Overview

There is an urgent need for low-cost, easy-to-use tools that can accurately predict adverse maternal and perinatal outcomes. A prediction model could assist in the management of adverse outcomes by allowing early identification of high-risk women and babies based on early manifestations of the diseases (signs and symptoms), which can guide the decision making for transfer and care in health facilities. Low- and middle-income countries with high burden of maternal mortality and morbidities may especially benefit from these simple technologies.

Our goal is to create a maternal, fetal, and newborn death prediction model integrated onto a single maternal and child health platform, supported by sensor technology (SpO<sub>2</sub>); ultimately converting the 'P' of PIERS, from PRE-EMPT's Objective 2, from "pre-eclampsia" to both "pregnancy" and "paediatric."

This study builds onto the success of the original PIERS on the Move project, completed in South Africa in 2014.

Through the funding from Grand Challenges Canada, we embarked on two projects:

- 1 A hypotension predictive modeling project in Pakistan
- 2 The development of a neonatal pulse oximeter

With these projects, we are ultimately aiming to incorporate a hypotension risk model and an accurate, simple to use neonatal pulse oximeter into the PIERS platform.

For the hypotension project, a prospective cohort study has been conducted at Jinnah Post Graduate Medical Center (JPMC), Karachi, Pakistan. We recruited women



who have admitted for delivery or are postpartum within forty-two days of delivery.

## Year 7 Progress

**Hypotension:** Recruitment to the prospective cohort at JPMC was concluded in 2016. Between July 15, 2016 and December 15, 2016, a total of 2,738 women were recruited to the study. Of these women, 13 (0.47%) had an adverse maternal outcome (death or severe morbidity) that occurred after recruitment and predictor data collection. This is significantly less than anticipated given our pre-study audit of the hospital population. In total, 198 (7.23%) women achieved a diagnosis of sepsis (170 of these met diagnostic criteria at the first study assessment) and 151 (5.51%) suffered a postpartum haemorrhage.

We were also able to collect a significant cohort of pulse oximetry data using the mobile application in this study.

ABOVE RIGHT: Hypotension study patient being evaluated at JPMC, Pakistan.

The raw photoplethysmogram (PPG) was recorded to facilitate the optimal estimation of heart rate, heart rate variability, oxygen saturation and other parameters that may be used to optimize future signal quality estimates and to develop novel methods to characterise and display the information contained in the PPG. These waveform characteristics will be combined with other clinical data to improve diagnostic accuracy in this population.

**Neonatal sensor development:** The neonatal sensor has been clinically evaluated against a range of leading commercial pulse oximetry brands in children undergoing elective anaesthesia. The performance is highly comparable to these commercial sensors. The neonatal sensors are compatible with the new android pulse oximetry module developed by LGT.

## Year 8 Deliverables

**Hypotension:** Samina Bakhtawar, Masters Student at Aga Khan University, Karachi, Pakistan has planned an analysis of risk factors for sepsis and septic shock in this study population using a nested case-control cohort study design.

Additional analysis of the complete prospective cohort is being led by Beth Payne, UBC, to test the hypothesis that we can develop a diagnostic model for maternal sepsis without laboratory parameters that could be used in a community health setting.

**Neonatal sensor:** We are planning to undertake regulatory testing and approvals of the neonatal sensors as soon as additional funding has been identified.



# Mapping Outcomes for Mothers (MOM)

**Principal Investigators:** Tabassum Firoz, Tatenda Makanga

**Trainee:** Yolisa Dube (Masters student)

**Funding:** Grand Challenges Canada, Bill & Melinda Gates Foundation

## Overview

Mapping Outcomes for Mothers (MOM) was conceived in 2012 with the main aim of elucidating the geographic influences on adverse maternal outcomes. As such, MOM contributes towards achieving a more precise public health approach that would allow policy makers to take targeted and individualized action at the community level to improve maternal health. We envisioned creating an integrated picture of local maternal health risk, using Geographical Information Systems (GIS) and spatial epidemiology to geo-visualize of the distribution and determinants of maternal health and outcomes.

## Year 7 Progress

### Scoping Review on the Use of GIS in Maternal Health

The scoping review set the stage for the thematic premise of the project leading to contribution of new methods for generating the framework GIS data essential for conducting geospatial analyses related to maternal health in low resource settings (Makanga PT et al. 2016). From this study, we found that GIS was mainly used to evaluating access to maternal care services and that are new opportunities for its use in elucidating community level maternal health risk (Makanga PT et al. 2016).

### Development of a New Geographical Model for Assessing Seasonal Variation in Access to Maternal Health Services

Using the baseline data, road quality data and weather records, a new geographical model for assessing the seasonal variation in access to maternal health services was developed for the CLIP Mozambique site (Makanga PT et al. 2016). This novel approach incorporates the daily transport realities that women will use to transit to care.

### Community Perspectives on the Determinants of Maternal Health in Rural Southern Mozambique

Using qualitative methods, we found that in rural southern Mozambique, community perceptions of determinants of maternal health included political, economic, socio-cultural and environmental factors (Firoz et al., 2016). These determinants were closely linked with one another and highlight the importance of including the local history, context, culture and geography in the design of maternal health programs.

### Development of the Initial MOM App

The findings of the qualitative study were used together with the baseline data from CLIP Mozambique to evaluate the community specific factors related to adverse maternal and perinatal outcomes (publication under preparation). All these data were used to design an initial version of the MOM app, which is intended for use by community health workers to better identify the community specific geographical factors that elevate risk for adverse maternal outcomes, and link women to local resources to potentially help with averting these risks.

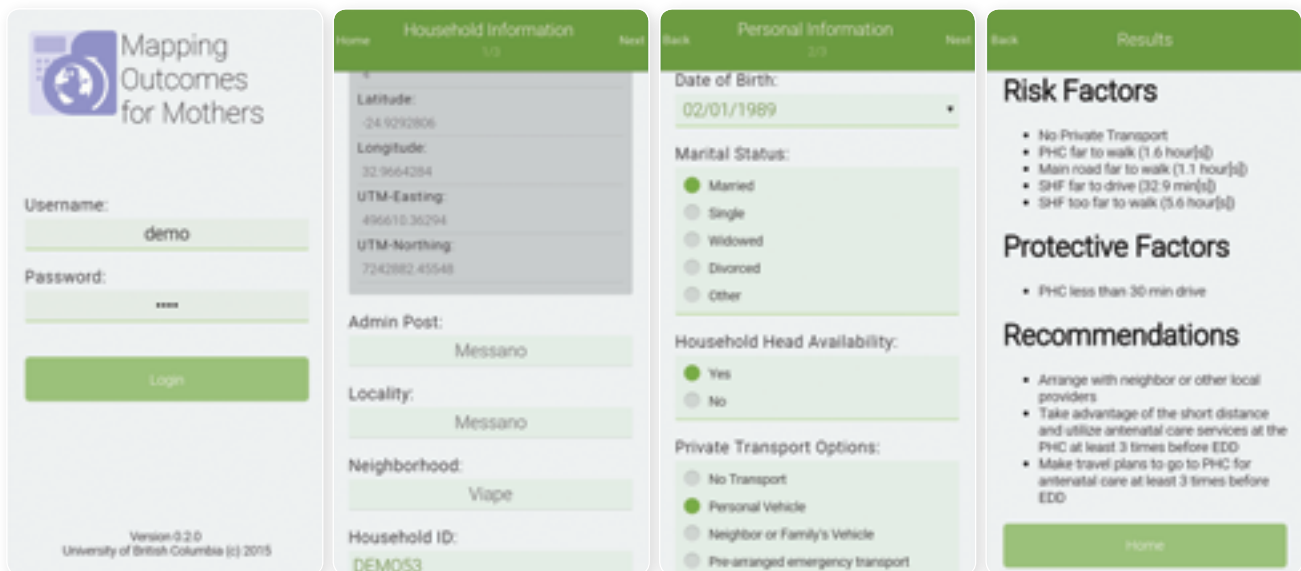
### Policy Impact

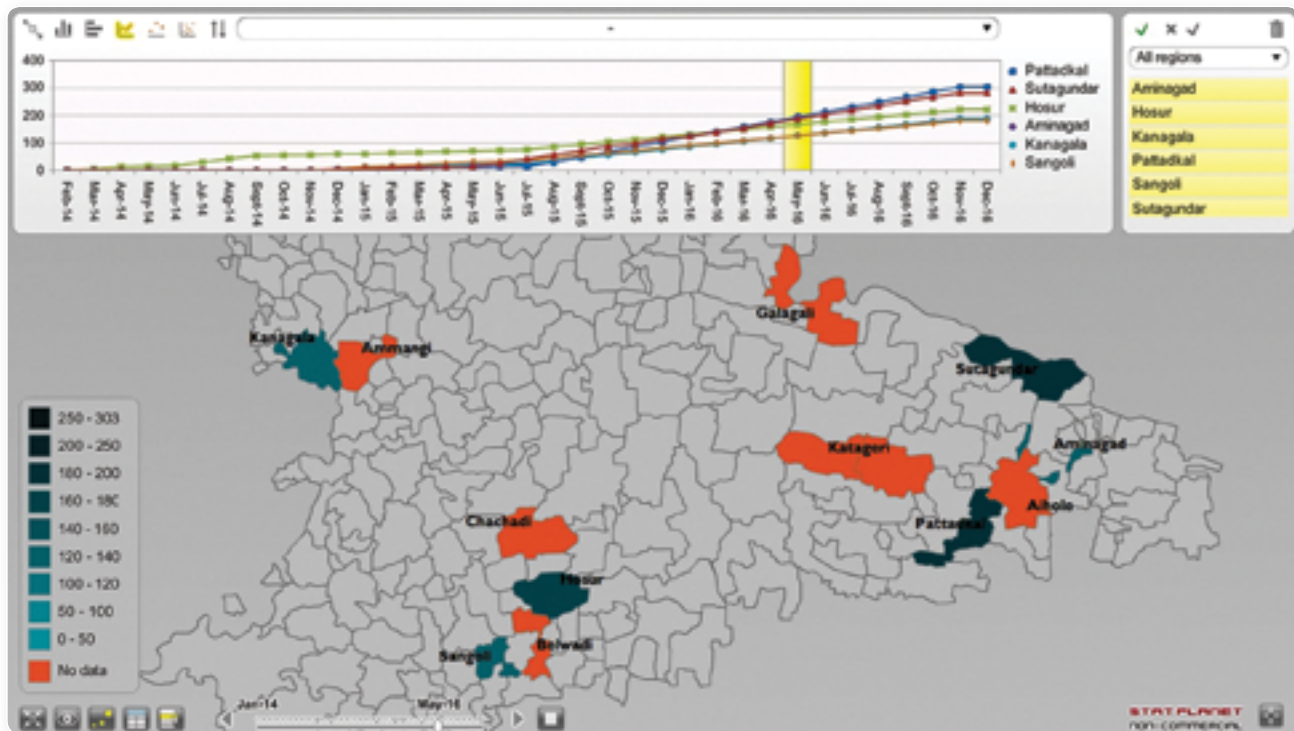
In the last year, the lessons from the MOM work have contributed to global maternal health policy outreach. As part of USAID's steering committee on mapping and reporting maternal deaths, MOM contributed to a publication for how Geographic Information System (GIS) could potentially be used as part of broader efforts for ending preventable maternal and newborn mortality (Molla et al., 2017). The MOM work was also presented to the First Nations Health Authority to illustrate how the lesson from Mozambique could be translated into the Canadian context to solve similar maternal health problems in rural and remote First Nations communities in British Columbia. This dialogue also contributed to a publication on reverse innovation in maternal health (Firoz T et al. 2017).



Tatenda was invited to a conference in Geneva hosted by the United Nations Office for Outer Space Affairs (UNOOSA) and the WHO to talk about the use of satellite data in modeling access to maternal care services in the

MOM project. This involvement contributed to high level policy recommendations for cooperation on the use of satellite technology in improving global health that will be discussed at the UNISPACE+50 conference in 2018.





## Year 8 Deliverables

GIS is being used in the MOM project to chart progress and impact of the CLIP Trials across the axes of time and space. The trial data are also being used to explore if women who had similar POM characteristics went on to experience different outcomes, and the extent to which geography could explain these differences. This is a first step towards integrating geography with the other mobile tools used in CLIP.

Ms. Yolisa Dube recently joined the MOM project as a research assistant and MPhil student at MSU. Yolisa (pictured) will be using outcomes and socio-demographic data from the CLIP Trials to describe the geographical patterns in adverse maternal outcomes and further elucidate the factors promoting maternal resilience.

## Publications

- Firoz T, Makanga PT, Nathan HL, Payne B, Magee LA. Reverse innovation in maternal health. *Obstet Med.* 2017
- Makanga PT, Schuurman N, Sacoor C, Boene HE, Vilanculo F, Vidler M, Magee L, Dadelszen P, Sevene E, Munguambe K, Firoz T. Seasonal variation in

geographical access to maternal health services in regions of southern Mozambique. *Int J Health Geogr.* 2017;16(1):1.

- Molla YB, Rawlins B, Makanga PT, Cunningham M, Ávila JE, Ruktanonchai CW, Singh K, Alford S, Thompson M, Dwivedi V, Moran AC. Geographic information system for improving maternal and newborn health: recommendations for policy and programs. *Pregnancy Childbirth.* 2017;17(1):26.
- Firoz T, Vidler M, Makanga PT, Boene H, Chiaú R, Sevene E, Magee LA, von Dadelszen P, Munguambe K. Community perspectives on the determinants of maternal health in rural southern Mozambique: a qualitative study. *Reprod Health.* 2016;13(2):112.
- Makanga PT, Schuurman N, Sacoor C, Boene H, Von Dadelszen P, Firoz T. Guidelines for creating framework data for GIS analysis in low-and middle-income countries. *Can Geogr.* 2016;60(3):320-32.
- Makanga PT, Schuurman N, von Dadelszen P, Firoz T. A scoping review of geographic information systems in maternal health. *Int J Gynecol Obstet.* 2016;134(1):13-7.

# fullPIERS (Pre-eclampsia Integrated Estimate of RiSk): External Validation, Recalibration and Added Value of a Novel Biomarker

**Principal Investigator:** Peter von Dadelszen

**Trainees (co-ordinator):** U. Vivian Ukah (PhD candidate), Beth Payne (Post-doctoral fellow), and Joost Akkermans (O&G resident)

**Funding:** Canadian Institutes of Health Research, European Union, British Columbia Children's Hospital Research

## Overview

The fullPIERS model was developed to quickly identify women at high risk of experiencing adverse outcomes from pre-eclampsia to manage them effectively. The model showed great potential upon internal validation as a predictive tool (AUC ROC 0.88) and requires external validation for implementation into clinical practice.

## Year 7 Progress

U. Vivian Ukah, a recipient of the UBC Four Year Fellowship, is undertaking the external validation, recalibration and addition of a new biomarker, placental growth factor (PIGF) to the fullPIERS model, for her PhD project.

Data collection for all the sites has been completed: British Columbia Women's Hospital, Canada, FINNPEC Finland data, PELICAN data, Alere-PETRA, the PREP UK study and the John Radcliffe Hospital, Oxford, UK.

Temporal and external validation of the fullPIERS model have been carried out using data collected from the BC Women's Health Centre and combined with the FINNPEC, PELICAN, Alere-PETRA, and Oxford datasets. The fullPIERS model retained good discriminatory performances, AUROC of 0.82 (95% CI 0.76–0.87) and AUROC of 0.81 (95% CI 0.75–0.86) for the temporal and external validations respectively. The calibration of the model was also fair although recalibration might improve its performance (see figures).

For the extension of the fullPIERS model with biomarker, PIGF was incorporated into the model using the PELICAN and PETRA studies, which measured maternal blood levels of PIGF. Our hypothesis that PIGF will improve the identification of women at risk of complications from

pre-eclampsia was not met as there was no significant improvement of the model upon extension with the biomarker.

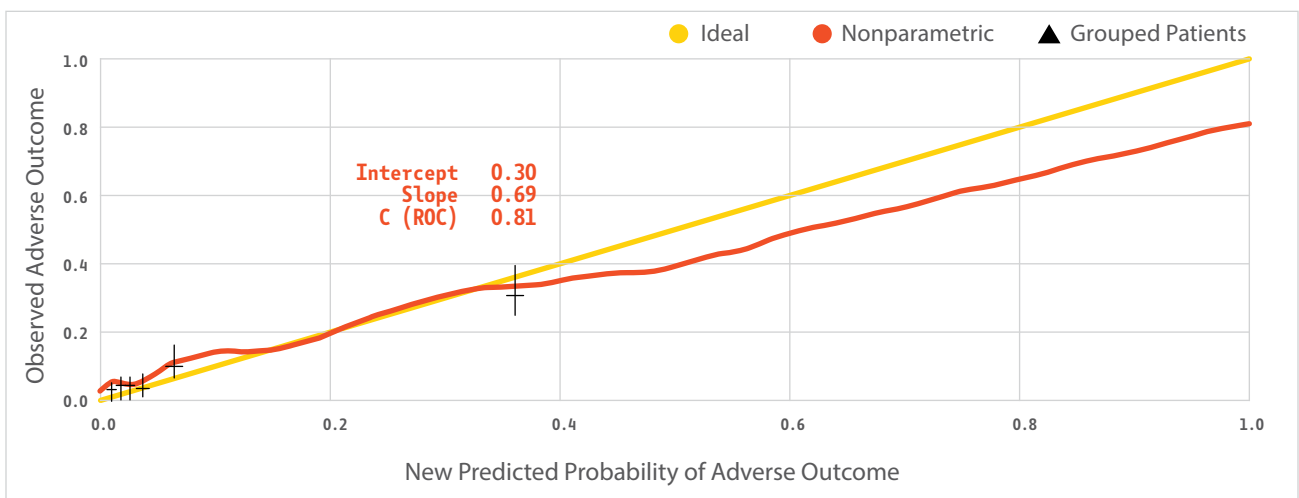
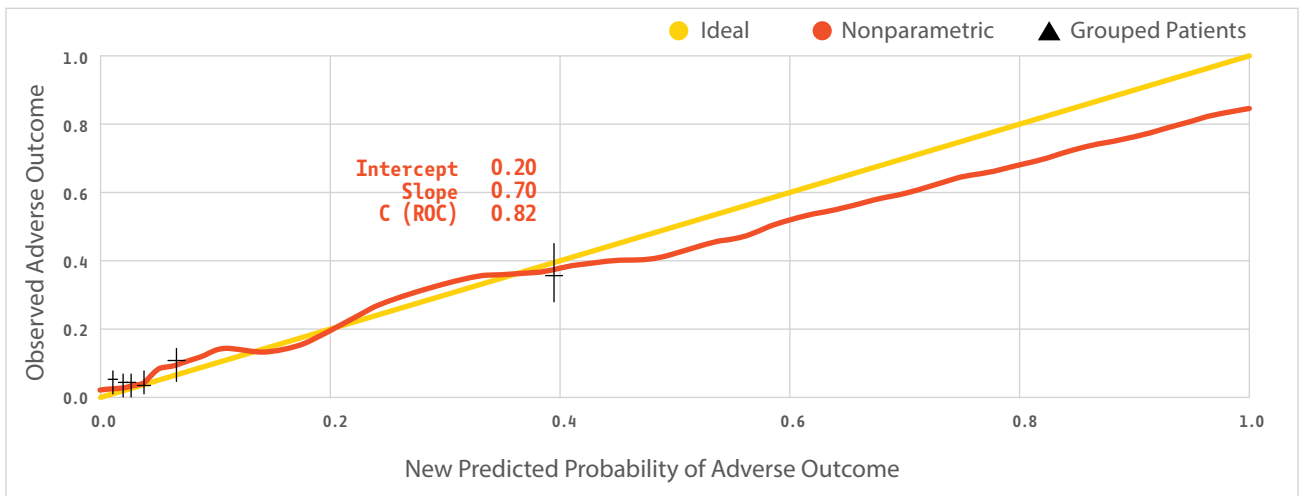
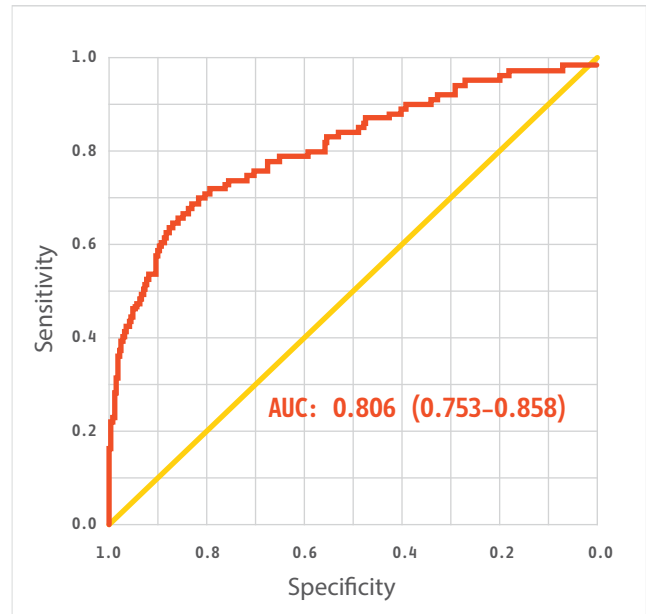
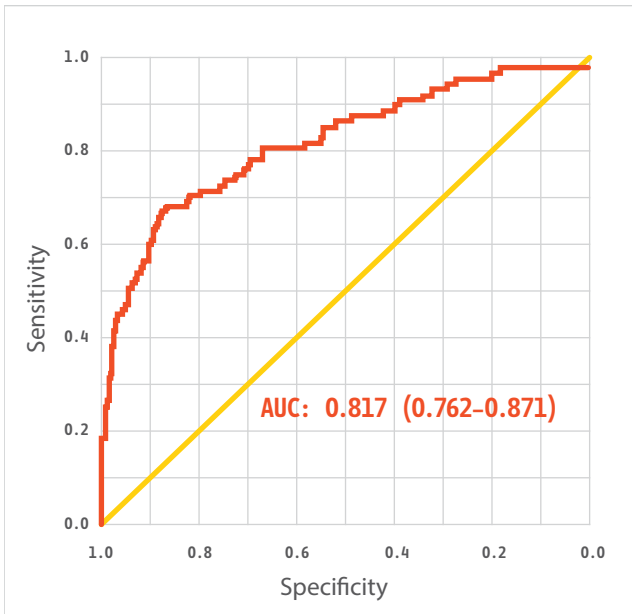
## Year 8 Deliverables

For the next year, we plan to finalise all data analyses and writing of manuscripts. Expected publications include:

- Temporal and external validation of the fullPIERS model using data collected from the BC Women's Hospital, Canada and the combined FINNPEC, Alere-funded PETRA, PELICAN and Oxford datasets.
- Assessing the incremental value of the addition of PIGF in the fullPIERS model.
- Recalibration of the fullPIERS model for better performance, in the context of a methodology paper, using external datasets.
- Domain validation of the fullPIERS model in women with early-onset pre-eclampsia using the combined PREP, Dutch- PETRA datasets.

## Publications and Presentations

- Ukah UV, Payne B, Lee T, Magee LA, von Dadelszen P. External validation of the fullPIERS model for predicting adverse maternal outcomes in pregnancy hypertension in low-and middle- income countries. *Hypertension*. 2017;116.
- Ukah UV, Mbofana F, Rocha BM, Loquiha O, Mudenyanga C, Usta M, Urso M, Drebit S, Magee LA, von Dadelszen P. Diagnostic performance of placental growth factor in women with suspected preeclampsia attending antenatal facilities in Maputo, Mozambique. *Hypertension*. 2017;69(3):469-74.



ABOVE TOP ROW: Discriminatory performance in  
 (A) Temporal dataset  
 (B) Primary external datasets.

ABOVE BOTTOM ROWS: Calibration graphs for the  
 (A) Temporal  
 (B) Primary external validation datasets for  
 adverse maternal outcomes occurring within  
 48hrs of admission.

# Collaborative Integrated Pregnancy High-Dependency Estimate of Risk (CIPHER)

**Principal Investigator:** Peter von Dadelszen

**Trainees (co-ordinator):** Helen Ryan and Beth Payne (Post-doctoral fellow)

**Funding:** Canadian Institutes of Health Research (pilot funding)

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## Overview

Most women who die during or soon after pregnancy die in an intensive care unit (ICU), if an ICU is available. Maternal ICU admissions follow both obstetric and non-obstetric complications in pregnancy. Approximately 0.25–1.5% of hospital admissions during pregnancy will require admission to the ICU. About two thirds of these admissions are due to obstetric causes (e.g. haemorrhage and pre-eclampsia) and one-third are due to maternal medical or surgical complications.

ICU clinical prediction models, including APACHE II, APACHE III, MODS, SAPS 3, and SOFA, were developed to assess the likelihood of an outcome, such as death or severe morbidity, in general ICU patient populations, as well as the severity of an individual patient's condition to guide care and counseling. However, most ICU outcome prediction models were designed in general critical care populations in high-income countries (HICs) and their use in obstetric populations and in low- and middle-income countries (LMICs) is contentious. Other than SOFA and the Maternal Severity Index rules, most general ICU prediction rules tend to overestimate the risk of death by up to 20-fold, and none have been developed to predict maternal death and prolonged organ support. We propose, that because of the unique physiology during pregnancy and postpartum, new pregnancy-specific clinical prediction rules are required. We have built on the expertise and experience in clinical prediction modeling from PIERS and developed a clinical prediction model that is applicable to any cause of maternal morbidity or mortality, in both low and high-income settings.

The Collaborative Integrated Pregnancy High-dependency Estimate of Risk (CIPHER) study developed and internally validated a clinical risk prediction model for maternal

mortality or severe maternal morbidity, for critically ill pregnant or recently delivered women in the ICU.

Following a survey of obstetric and ICU facilities in both HIC and LMIC sites to ensure suitability of each site, 13 collaborating sites with intensive care units from 11 countries were enrolled. Data were collected through a retrospective chart review at each participating institution.

Women were included if they were admitted to a critical care unit for greater than 24 hours and were known to be either pregnant (either before or detected during their ICU stay) or less than 42 days following the end of the pregnancy, irrespective of pregnancy duration from 1 January 2000 – 31 December 2012. Women admitted for less than 24 hours or who were neither pregnant nor recently-pregnant were excluded.

The composite primary outcome was defined as maternal death either during pregnancy or within 42 days of the end of pregnancy, prolonged duration of organ support for more than 7 days, requirement of  $\geq 5$  units of blood product, or hysterectomy for uncontrollable haemorrhage or uterine infection.

Predictor variable selection involved literature review to identify all potential candidate predictors followed by an iterative process of evaluation and consultation within the study working group to identify a set of the 12 most clinically-relevant, available and non-correlated variables were selected for final model development. Missing data were dealt with using imputation (MICE method). Women with missing outcome data or having at least seven of the 12 selected candidate predictor variables missing were excluded. Backward selection logistic regression was used to select final predictor variables in each of the ten imputed datasets based on significant reduction in AIC. A pooled

estimate of effect for the final variables was then generated using Rubin's rules.

The final CIPHER model includes: maternal age, surgical status in the preceding 24 hours, Glasgow Coma Scale, systolic blood pressure, total bilirubin, serum creatinine, activated partial thromboplastin time (aPTT) and white blood cell count. It is a simple model, including only 8 predictors, yet it still maintains high discrimination (AUC ROC 0.819 (95% CI 0.781 – 0.858)) and good calibration (calibration slope of 0.926 (95% CI 0.9193 - 0.9329) and intercept of -0.0881 (95% CI -0.1108 - -0.0655)) after internal validation. This model is novel and represents an improvement in performance of existing critical care outcome prediction models within this population.

All sensitivity and subgroup analyses demonstrated similar discriminative performance of the CIPHER model. When the CIPHER model was used to predict maternal death alone, the AUC ROC was 0.882 (95% CI 0.853 – 0.921). When the cohort was restricted to only those cases admitted to ICU during the antenatal and intrapartum period, or the postpartum period, the AUC ROC were estimated as 0.854 (95% CI 0.793 – 0.910) and 0.842 (95% CI 0.791 – 0.879), respectively. Similarly, when the cohort was restricted to either only cases collected at low and middle income country facilities or high-income country facilities the AUC ROC were estimated to be 0.851 (95% CI 0.812 – 0.894) and 0.774 (95% CI 0.663 – 0.868), respectively.

The CIPHER model determines the risk of death and/or prolonged duration of organ support in a population of pregnant and recently-pregnant women receiving critical care, with similar clinical utility in both HICs and LMICs. CIPHER has the potential to be a pragmatic risk prediction tool to identify women at highest risk for adverse outcomes who require more aggressive management and to assist

with decisions regarding management and timing of delivery. Ultimately, once validated, the CIPHER tool could be applied globally to reduce the burden of pregnancy-related morbidity and mortality.

## Year 7 Progress

The CIPHER collaborative group worked together to re-develop the CIPHER model based on reviewer feedback from the original manuscript submission to Critical Care Medicine in 2016. The primary change in the model development process came from updates to the methodology used to deal with missing data. This work has resulted in a revised manuscript of the final model now submitted for publication with BJOG. These updated results are shared above in the study summary.

## Publications

- Payne BA, Ryan HM et al. Precision medicine for pregnant and recently-pregnant women receiving critical care: development of the CIPHER (Collaborative Integrated Pregnancy High-dependency Estimate of Risk) model. *Br J Obstet Gynaecol*. (submitted 07/2017)
- Ryan HM, Sharma S, Magee LA, Ansermino JM, MacDonell K, Payne BA, Walley KR, von Dadelszen P. The usefulness of the APACHE II score in obstetric critical care: a structured review. *J Obstet Gynaecol Can*. 2016;38(10):909-18.
- Aarvold AB, Ryan HM, Magee LA, von Dadelszen P, Fjell C, Walley KR. Multiple organ dysfunction score is superior to the obstetric-specific sepsis in obstetrics score in predicting mortality in septic obstetric patients. *Critl Care Med*. 2017;45(1):49.

# Placental Growth Factor in Mozambique

**Principal investigators:** Peter von Dadelszen, Beatriz Manriquez Rocha

**Trainee (co-ordinator):** U. Vivian Ukah (PhD candidate)

**Funding:** Irish Aid Mozambique, Government of Flanders, Microlife, Clinton Health Access Initiative Maputo

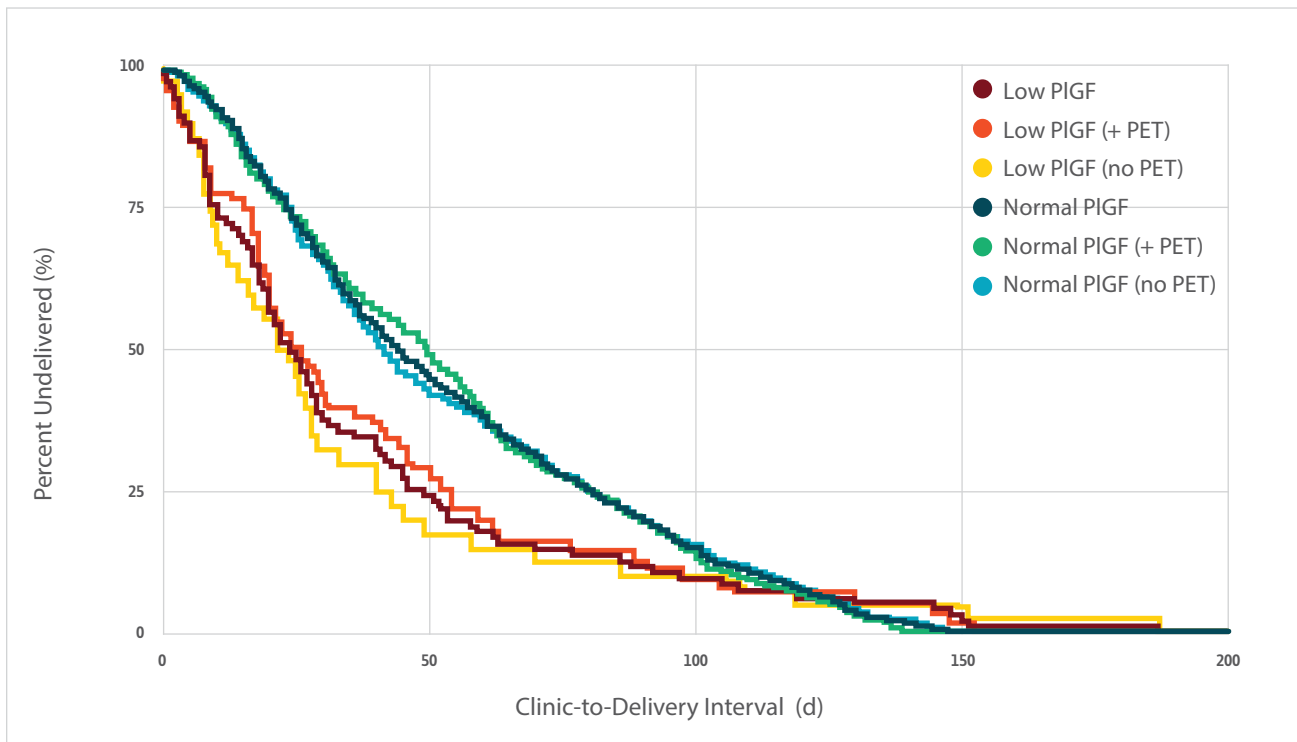
## Overview

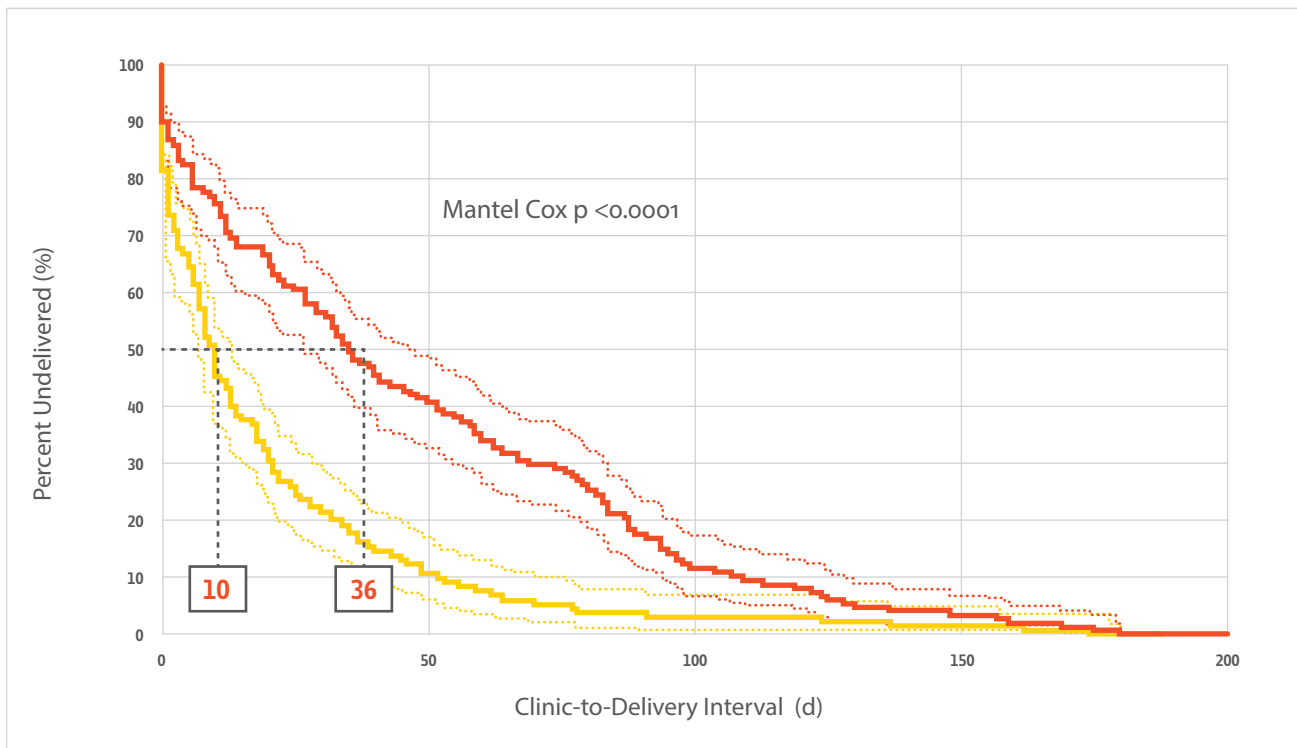
As a new element of the Monitoring objective within PRE-EMPT, and in association with CoLab, we have been partnering with the Mozambique team of the Clinton Health Access Initiative to (i) assess the diagnostic performance of PIGF in clinics in Maputo and (ii) pilot its clinical implementation in Maputo. These two projects, one of which was published in *Hypertension* earlier this year and the other has also been submitted to the same journal, are major steps forwards in assessing the real-world applicability of this potentially frame-shifting test.

The first published project was a blinded, prospective cohort study of maternal plasma PIGF in women with

suspected pre-eclampsia was conducted in antenatal clinics in Maputo, Mozambique. The primary outcome was the clinic-to-delivery interval. Other outcomes included: confirmed diagnosis of pre-eclampsia, transfer to higher care, mode of delivery, intrauterine fetal death, preterm birth, and low birth weight.

Of 696 women, 95 (13.6%) and 601 (86.4%) women had either low (<100 pg/mL) or normal ( $\geq 100$  pg/mL) plasma PIGF, respectively. The clinic-to-delivery interval was shorter in low PIGF, compared with normal PIGF, women (median 28 days [interquartile range, 15–58] versus 48 [26–87],  $P < 0.0001$ ). In both groups, this was consistent between women who were adjudicated to have and have not developed pre-eclampsia. In addition, women with





low PIGF were more likely to have a confirmed diagnosis of pre-eclampsia, have higher BP, have higher serum creatinine concentrations, be transferred for higher care (particularly to a referral centre), deliver 2 weeks earlier (although usually at term), deliver within 7 and 14 days, deliver by Caesarean section, and suffer perinatal losses than women with normal PIGF. Birth weights tended to be lower in women with low PIGF, but the observed 200 g difference did not reach the prespecified level for statistical significance ( $P=0.0129$ ). For women with hypertension (compared with those without, irrespective of PIGF concentration), the clinic-to-delivery intervals were 44 days (21–77) and 39 days (22–78.5), respectively ( $P=0.8670$ ).

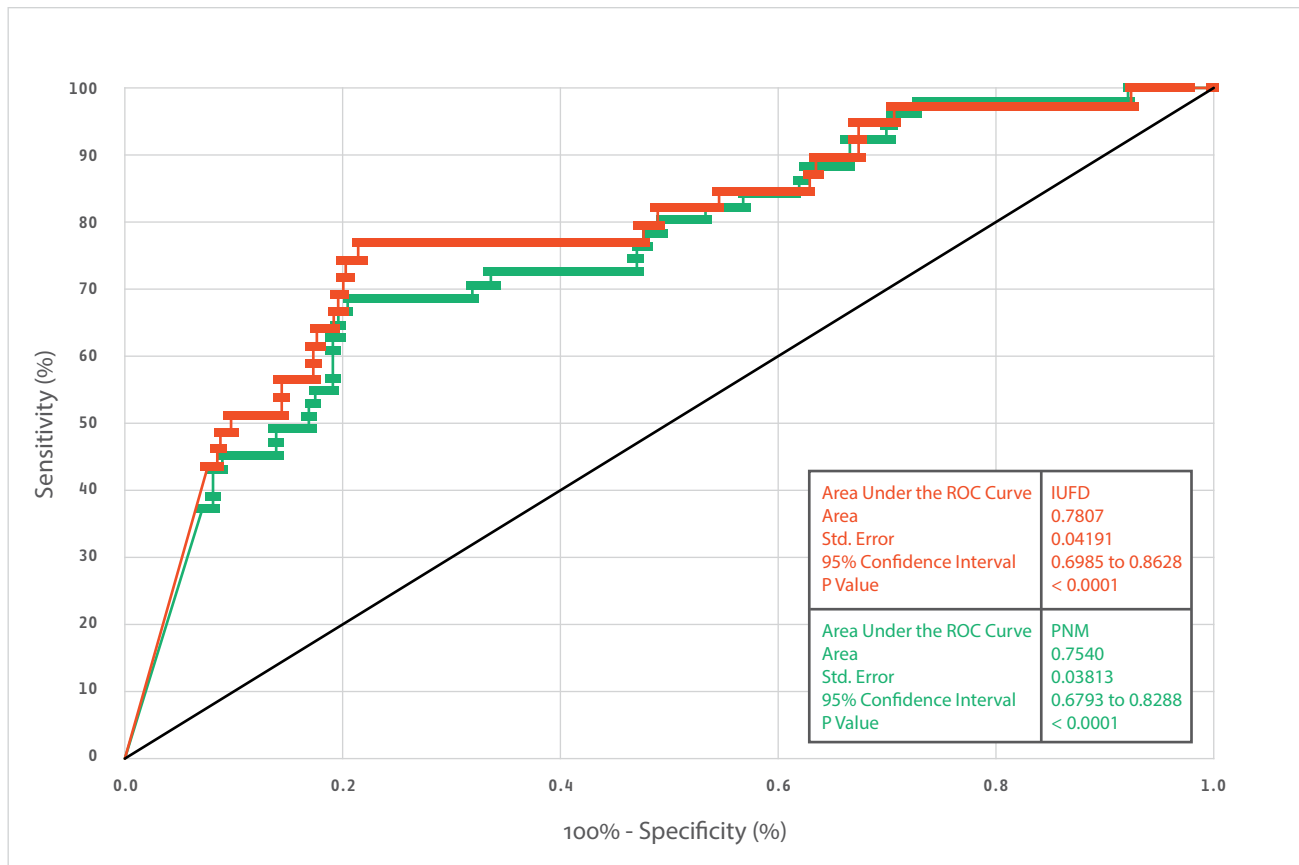
When comparing groups between women with either normal or low PIGF and either confirmed pre-eclampsia or not, differences between the PIGF groups were confirmed ( $P<0.01$ ), but no differences were observed within either normal or low PIGF whether or not women had a confirmed diagnosis of pre-eclampsia ( $P\geq 0.01$ ), by Kruskal–Wallis and Dunn analyses.

Therefore, in urban Mozambican women with symptoms or signs suggestive of pre-eclampsia, low maternal plasma PIGF concentrations are associated with increased risks of adverse pregnancy outcomes, whether the diagnosis of pre-eclampsia is confirmed. Therefore, PIGF should improve the provision of precision medicine to individual women and improve pregnancy outcomes for those with pre-eclampsia or related placenta-mediated complications.

The second project was an operational pilot implementation of maternal plasma PIGF in women with suspected pre-eclampsia conducted in six antenatal clinics in Maputo, Mozambique (six control clinics for comparison). The primary outcome was transfer to higher levels of care, following the informative PIGF assay.

Of antenatal visits, 133/31,993 (0.42%) and 20/33,841 (0.06%) resulted in a transfer of care for women attending intervention and control clinics, respectively ( $p < 0.0001$ ). The clinic-to-delivery for women with low PIGF (<100 pg/ml) interval was shorter, (vs normal PIGF (median 10 days [IQR 1 - 25] vs 36 [11 - 83],  $p < 0.0001$ )).

ABOVE: Kaplan-Meier survival curve of clinic-to-delivery interval between women with normal and low maternal plasma placental growth factor in the operational pilot implementation study. Women with low placental growth factor (PIGF) had shorter clinic-to-delivery intervals (median 10) compared with women with normal PIGF (median 36 days).



Low PIGF was associated with younger maternal age, higher blood pressure, earlier delivery, more therapeutic interventions, preterm birth, lower birth weight, and perinatal loss.

In addition, one-third of hypertensive women with PIGF < 50 pg/ml suffered a stillbirth. The area under the receiver-operator curve analysis of the performance determined that maternal PIGF predicted both intrauterine fetal death (AUC ROC = 0.78) and perinatal death (AUC ROC = 0.75). Using a cut-off of <50 pg/ml, maternal plasma PIGF has a sensitivity of 76.9% (95% CI 60.7% - 88.9%) and specificity of 74.1% (95% CI 68.0% - 79.5%).

Therefore, in urban Mozambican women with symptoms and/or signs suggestive of pre-eclampsia, low maternal plasma PIGF concentrations are associated with increased risks of adverse pregnancy outcomes, especially early delivery and stillbirth. Introducing PIGF into the clinical care of women with suspected pre-eclampsia

was associated with increased transfers to higher levels of care; low PIGF (<100 pg/ml) was associated with increased maternal and perinatal risks. PIGF <50 pg/ml is particularly associated with stillbirth in women with suspected pre-eclampsia.

## Publications

- Ukah UV, Mbofana F, Rocha BM, Loquiha O, Mudenyanga C, Usta M, Urso M, Drebit S, Magee LA, von Dadelszen P. Diagnostic performance of placental growth factor in women with suspected preeclampsia attending antenatal facilities in Maputo, Mozambique. *Hypertension* 2017;69(3):469-474.
- Manriquez Rocha B, Mbofana F, Loquiha O, Mudenyanga C, Ukah UV, Magee LA, von Dadelszen P. Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique. *Hypertension* (submitted)

# Extension of the fullPIERS Model with Placental Growth Factor (PIGF) for Prognosis in Women with Pre-eclampsia

**Principal Investigator:** Peter von Dadelszen

**Trainee (co-ordinator):** U. Vivian Ukah (PhD candidate)

**Funding:** Canadian Institutes of Health Research (CHIR), Bill & Melinda Gates Foundation (through CoLab)

## Placental Growth Factor (PIGF) as a Marker of Fetal Growth Restriction Caused by Placental Dysfunction

### Introduction

The fullPIERS model showed a good discrimination for women with pre-eclampsia with AUROC of 0.88 upon development and 0.81 upon external validation using a combination of cohorts from tertiary centres in high income countries (HICs). Several studies have that PIGF, which is measurable in the maternal circulation, might be a useful prognostic marker in pre-eclampsia. Expectantly managing women with pre-eclampsia can be a challenge since the woman remains at risk of severe complications. The ability to improve the discrimination between the women who will develop adverse maternal outcomes and those who will not will aid in more effective management of these women. Thus, the extension of the fullPIERS model with PIGF was carried out to assess if the biomarker would add any incremental value to the model.

### Methods

Plasma PIGF was measured in women presenting with suspected pre-eclampsia at sites in the United States of America and Canada (Alere PETRA data), and the United Kingdom (PELICAN data). The data was restricted to women with pre-eclampsia with available PIGF measurements within 14 days of admission. PIGF measurements were converted to percentiles for normal reference range by gestational age interval. The univariable discriminatory performance of PIGF for predicting adverse maternal outcomes within 48 h of admission was assessed. The ability of PIGF to predicting adverse fetal outcomes

occurring within 7 days, 14 days and at any time from admission with pre-eclampsia was also assessed.

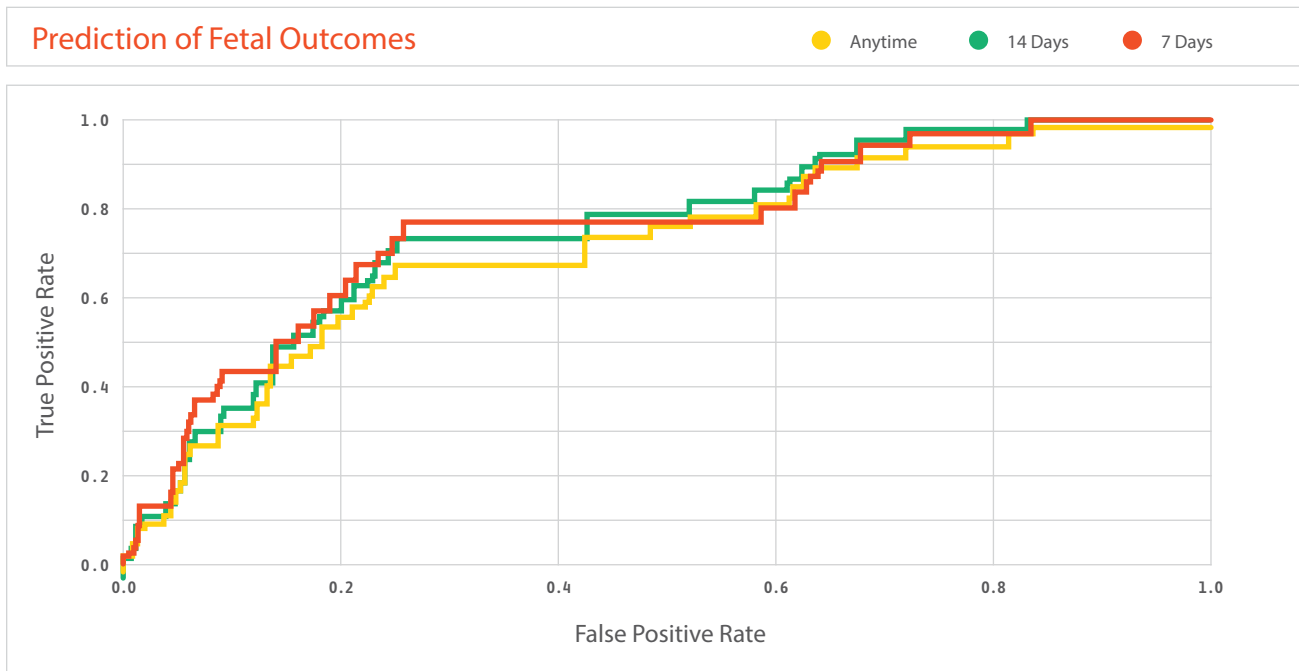
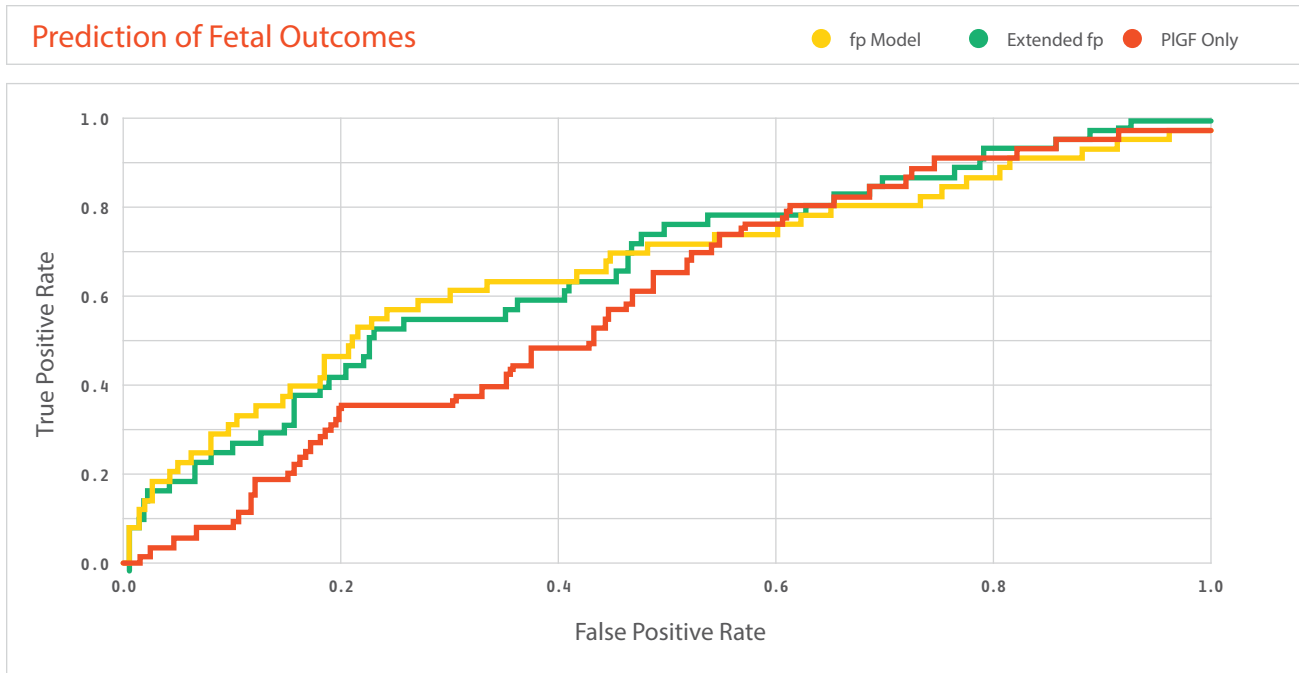
Before addition of PIGF to the fullPIERS model, the original model performance in this cohort was assessed.

### Results

PIGF showed a poor discriminatory performance for the prediction of adverse maternal outcomes within 48 hours of admission (AUROC of 0.60 (95% CI 0.52-0.67)) although it performed well in predicting adverse fetal outcomes (admission into NICU for 48 h or more) within 7 days, 14 days and at any time, with AUROCs of 0.76 (95% CI 0.67-0.85), 0.75 (95% CI 0.67-0.83), and 0.72 (95% CI 0.64-0.80), respectively. The original fullPIERS model also performed poorly in this cohort with AUROC of 0.67 (95% CI 0.58-0.76) and addition of PIGF to the model did not improve the discriminatory performance of the model, AUROC of 0.67 (95% CI 0.59-0.75).

### Discussion

The fullPIERS model and addition of PIGF to the model did not improve its prognostic ability for adverse maternal outcomes in this cohort. A possible reason for the poor performance is that the women in this cohort were less likely to be managed expectantly compared to the development cohort. Therefore, they are more likely to be delivered earlier, which does not allow enough time for prediction. In general, PIGF had a poor prognostic ability for the prediction of adverse maternal outcomes for women admitted with pre-eclampsia, but PIGF appeared to discriminate well for women with composite fetal outcomes, especially for women admitted before 35 weeks of gestation.



ABOVE TOP: Prediction of adverse maternal outcomes using (i) only PIGF (ii) original fullPIERS (fp) model and (iii) the extended fullPIERS model with AUROC of 0.60 (95% CI 0.52-0.67), 0.67 (95% CI 0.58-0.76), and 0.67 (95% CI 0.59-0.75), respectively.

ABOVE BOTTOM: Prediction of fetal outcomes occurring within 7 days, 14 days and any time from admission with pre-eclampsia with PIGF with AUROCs of 0.76 (95% CI 0.67-0.85), 0.75 (95% CI 0.67-0.83), and 0.72 (95% CI 0.64-0.80), respectively.

# Economic Evaluation of the CLIP Trials

**Principal Investigator:** Peter von Dadelszen, Craig Mitton

**Trainee (co-ordinator):** Asif Raza Khowaja (PhD candidate)

**Funding:** Bill & Melinda Gates Foundation, Aga Khan Development Network

## Overview

Economic evaluation of Community Level Interventions of Pre-eclampsia (CLIP) is an integral component of the trial, to inform policy decisions about the allocation of resources for the potential of post-trial programme scale-up. Using a societal perspective, we are interested in determining the costs to the health care system and to families of pregnant women in the intervention and control clusters. A mixed-methods approach (focus groups and cost-effectiveness analyses) will inform the design of the economic model, which allows us to understand the contextual cost drivers and conduct cost-effectiveness analyses. The results will provide support to decision makers who are considering the evidence of economic value and the effectiveness of the CLIP package of interventions. Economic evaluation of the CLIP Trials takes place in three CLIP countries, Pakistan, India and Mozambique.

## Year 7 Progress

The following activities were undertaken during the period of 2016-2017, in respective CLIP countries:

### Cost of Implementing CLIP Pakistan Trial

The financial costs were estimated for resources used in the start-up and implementation of the CLIP Trial in Sindh, Pakistan. The analytical perspective was that of the government funded National Lady Health Workers (LHWs) Program. The total financial costs were determined using an ingredients approach, whereby unit costs were multiplied with quantities of clinical items and mobile health (mHealth) devices. The capital costs were annualised over a period of 10 years, at a discount rate of 3%. Probabilistic analyses (i.e. Monte Carlo simulation) were performed to address cost uncertainties and 95% credible intervals were calculated. Marginal analyses were conducted to estimate

cost variation with hypothetical coverage expansion, the manuscript draft is in-review by co-authors.

### Maternal and Newborn Health Facility Costs-CLIP Pakistan Trial

A total of 31 eligible health providers and facilities (n= 25 in private; n=7 in public) were included in the final analysis in Pakistan. The unit costs of maternal and newborn health (MNH) services were determined through a simultaneous allocation method in the public facilities; and patient billing department in the private facilities. Descriptive analyses were performed, and analyses of variance (ANOVA) test applied to compare overall mean costs both within and between health facilities. A manuscript draft has been submitted to PLOS-One.

### Maternal and Newborn Health Facility Costs-CLIP India Trial

The CLIP India Trial recruitment was completed as of November 2016; and data on health resource use was captured as part of data collection during the trial. In addition, we have collected a wide range of maternal and newborn health services costs at 60 and 6 public health facilities. The unit costs of MNH services were determined through a simultaneous allocation method in the public facilities; and patient billing department in the private facilities. Descriptive analysis was completed; and shared with the site investigators. Manuscript draft is in-progress by site investigators.

### Economic Evaluation of CLIP Mozambique Trial

The site investigators have submitted an ethics amendment request at the institutional level for economic analysis of the CLIP Mozambique Trial.



ABOVE LEFT: An Accredited Social Health Activist (ASHA) discusses the signs and symptoms of pre-eclampsia and eclampsia from the CLIP India Trial.

ABOVE RIGHT: A labour room in a health facility in a CLIP Pakistan Trial site in Sindh Province.

ABOVE BOTTOM: Accredited Social Health Activists (ASHA), pictured here, are one of the cadres of health workers responsible for implementing the CLIP India Trial.

## Year 8 Deliverables

**CLIP Pakistan Trial:** Having completed the data consistency and quality checks, we will apply statistical analysis to estimate-and-compare mean costs for health resource utilization between intervention and control groups. Economic analysis (i.e., a mixed model inclusive of decision analysis and multi-state Markov) will be performed to calculate the incremental cost-effectiveness ratio (ICER) per disability-adjusted life years (DALYs) averted. Additionally, a probabilistic analysis will be performed to address costs and outcome related uncertainties. A project report, inclusive of key findings, will be shared with stakeholders.

**CLIP India Trial:** The current data on patient level costs (i.e., out-of-pocket costs) from the MNH registry are limited to direct-health facility utilization. We further aim to estimate societal costs, inclusive of opportunity costs as a result of hypertensive disorders of pregnancy- and other pregnancy- related illnesses. Site investigators are considering conducting a two-stage cluster rapid survey, using a population proportion to size sampling in the six clusters of the CLIP India Trial. Data will be analysed to estimate-and-compare mean costs using societal perspective. Later, the costs and trial outcome parameters will be modelled to calculate the incremental cost-effectiveness ratio (ICER) per disability-adjusted life years (DALYs) averted.

**CLIP Mozambique Trial:** The site investigators have submitted an ethics amendment request at the institutional level to collect data on unit costs for MNH services at various levels of the health system; and a few focus groups to understand/explore opportunity costs (time/productivity losses). Data will be analysed to estimate-and-compare mean costs using societal perspective. Later, the costs and trial outcome parameters will be modelled to calculate the incremental cost-effectiveness ratio (ICER) per disability-adjusted life years (DALYs) averted.



## Publications

- Khowaja AR, Mitton C, Qureshi R, Bryan S, Magee LA, von Dadelszen P, Bhutta ZA. Societal perspective on cost drivers for health technology assessment in Sindh, Pakistan. *Int J Technol Assess Health Care*. 2017;1-7.
- Asif Khowaja, presented the 'Societal perspective on cost drivers for health technology assessment in Sindh, Pakistan' (listed above) at the Health Technology Assessment International 2017 annual meeting in Rome, Italy



ABOVE: Elders from 3 de Fevereiro meet with the research team as part of the CLIP Mozambique Trial.

Objective



Treatment

# Objective 3: Timeline

## CLIP

- OCT 31 2013 — OCT 31 2014 — ○ CLIP India baseline survey
- JUN 01 2013 — SEP 31 2013 — ○ CLIP Pakistan baseline survey
- NOV 01 2013 — FEB 01 2014 — ○ Nigeria baseline survey (pilot clusters only)
- FEB 01 2014 — OCT 31 2014 — ○ CLIP India Pilot Trial
- MAR 10 2014 — OCT 10 2014 — ○ CLIP Mozambique baseline survey
- MAR 01 2014 — MAY 05 2015 — ○ CLIP Nigeria Pilot Trial
- FEB 01 2014 — OCT 31 2014 — ○ CLIP India Pilot Trial
- NOV 01 2014 — OCT 31 2016 — ○ CLIP India Definitive Trial
- FEB 07 2014 — JAN 18 2015 — ○ CLIP Pakistan Pilot Trial
- JAN 19 2015 — DEC 31 2016 — ○ CLIP Pakistan Definitive Trial
- FEB 24 2015 — FEB 24 2017 — ○ CLIP Mozambique Definitive Trial
- MAY 06 2015 — JAN 31 2016 — ○ CLIP Nigeria Definitive Trial



## 2012

- JUN 01 2012 — ○ Meetings held with stakeholders and community prior to launch of the CLIP Trial in Nigeria
- OCT 22 2012 — ○ Launch of CLIP India Trial in Karnataka, India
- NOV 01 2012 — ○ Mozambique is added as a fourth CLIP site



## 2013

- JUL 01 2013 — ○ Health workers are trained for CLIP Trials in India, Pakistan and Nigeria
- SEP 17 2013 — ○ CLIP Pakistan Trial launch and first CME event is held
- NOV 01 2013 — ○ CLIP Feasibility Study results shared for India, Pakistan and Nigeria at the Third Annual PRE-EMPT Meeting in New Delhi

## 2014

- JAN 28 2014 — ○ CLIP India Pilot Trial launch and meeting with stakeholders
- FEB 01 2014 — ○ Continuous professional development activities are held in CLIP India sites
- NOV 01 2014 — ○ Fourth Annual PRE-EMPT meeting, CLIP Pilot Trial interim results shared for India, Pakistan and Nigeria at the Fourth Annual PRE-EMPT Meeting in Seattle



## 2015

- JAN 01 2015 — ○ Electronic data capture begins in the CLIP Pakistan Trial
- APR 13 2015 — ○ The CLIP Trial protocol is published in the *Lancet*
- OCT 01 2015 — ○ CLIP Pilot Trial results shared for India, Pakistan and Nigeria at the Fifth Annual PRE-EMPT Meeting in Vancouver

## 2016

- MAY 30 2016 ○ CLIP Pakistan team meets with Government of Sindh representatives to discuss progress of the CLIP Trial
- JUN 01 2016 ○ Select communities in Maputo and Gaza develop a plan to raise and manage funds for transport in medical emergencies
- JUN 02 2016 ○ The second CME event takes place for medical professionals in Isra, Hyderabad
- JUN 08 2016 ○ First supplement for the CLIP Feasibility Study in *BMC Reproductive Health* titled "Community insights from four LMICs into normal and complicated pregnancies" is published
- JUL 11 2016 ○ The CLIP team meets with the Mozambican Ministry of Health
- SEP 30 2016 ○ Second supplement for the CLIP Feasibility Study published in *BMC Reproductive Health* "Building community-level resilience for care of women with pre-eclampsia"



## 2017

- JAN 20 2017 ○ CLIP India Baseline Study results published in *PLoS One*
- MAR 01 2017 ○ CLIP India Trial close-out site visit
- JUN 01 2017 ○ Meeting with the Director of Public Health in Mozambique to discuss reflections from the CLIP Mozambique Trial
- JUL 01 2017 ○ Meeting with Government stakeholders in Delhi to discuss reflections from the CLIP India Trial
- JUL 01 2017 ○ Meeting with Government stakeholders in Pakistan to discuss reflections from the CLIP Pakistan Trial



## Gynuity Oral Antihypertensive Trial

- JAN 01 2014 ○ Completion of Gynuity Oral Antihypertensive Trial pilot study enrollment
- OCT 01 2014 ○ Presentation of Gynuity Oral Antihypertensive Trial pilot findings at ISSHP World Congress
- APR 01 2015 ○ Start of Gynuity Oral Antihypertensive RCT enrolment
- SEP 01 2017 ○ Completion of Gynuity Oral Antihypertensive RCT enrollment

# Gynuity Health Projects Oral Antihypertensive Trial

**Principal Investigators:** Hillary Bracken, Tom Easterling

**Country Principal Investigator:** Shuchita Mundle

**Funding:** Bill & Melinda Gates Foundation

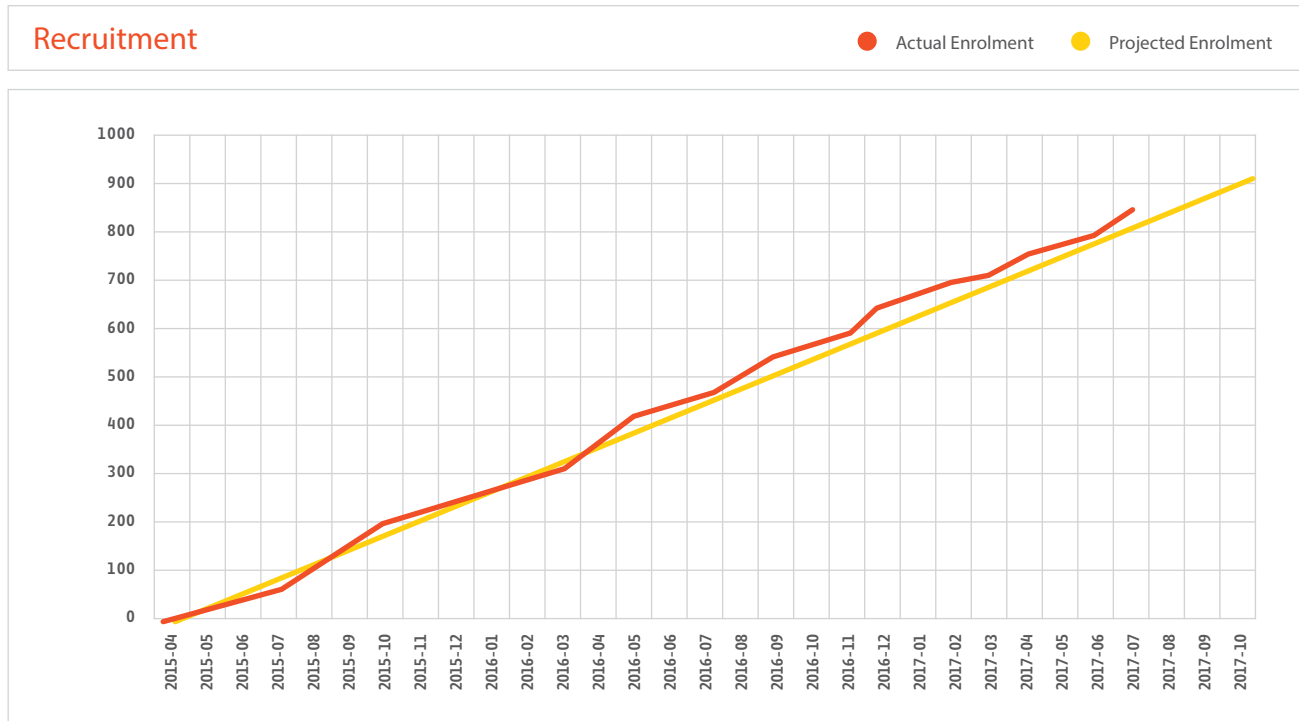
## Overview

Gynuity Health Projects, in collaboration with colleagues at Government Medical College, Nagpur and Daga Women’s Hospital, are conducting a pragmatic, open-label, randomised control trial of three oral antihypertensive regimens for women with severe hypertension in pregnancy. Women presenting with severe hypertension will be randomised to one of three oral regimens: nifedipine, labetalol or methyldopa. This trial will compare the efficacy, safety and side effects of these three oral regimens for management of severe hypertension in pregnant women. We hypothesise that nifedipine

treatment of severe hypertensive parturient women is more effective than treatment with either labetalol or methyldopa in controlling high blood pressure within six hours. The study will enrol 894 women at the two study sites in Nagpur, India: Government Medical College (GMC) and Daga Women’s Hospital.

## Year 7 Progress

Enrolment started in April 2015. As of July 2017, 832 women have been enrolled (GMC: 418; Daga: 437). We anticipate trial enrolment will be complete in September 2017.





ABOVE: Oral Antihypertensive Trial study team, Daga Women's Hospital.

# Community Level Interventions for Pre-eclampsia (CLIP) Trials

**Principal Investigators:** Peter von Dadelszen, Zulfiqar Bhutta, Laura Magee

**Trainee:** Marianne Vidler (PhD)

**Co-ordinator:** Sumedha Sharma

**Funding:** Bill & Melinda Gates Foundation

## Overview

Components of the CLIP Trial included community engagement, regular monitoring of pregnancies by community health care providers, community-level treatment with magnesium sulphate and oral methyldopa and recommendation for referral to higher level health facilities for identified high risk women.

The goal of the CLIP Trials is to reduce pre-eclampsia-related, and all-cause, maternal and perinatal mortality and major morbidity by 20% or more in intervention clusters in sub-Saharan Africa (Mozambique, MMR:489), and South Asia (India, MMR: 174 and Pakistan, MMR: 178). In Nigeria, the CLIP Trial ended recruitment shortly after the Pilot Trial; and the data from the intervention and study logs are being used for the process evaluation of the CLIP Nigeria Trial.

## Year 7 Progress

This past year marked the end of active recruitment and surveillance activities of the CLIP Trials with over 77,000 pregnancies recruited across three sites. During the life of the trials, more than 151,860 CLIP antenatal and postnatal visits have taken place in women's homes. Another component of the CLIP intervention was engagement of the community with the intended aim of improving birth preparedness, care-seeking and knowledge related to the hypertensive disorders of pregnancy.

These sessions were structured in a context-specific and culturally appropriate manner by the trial site-teams, and ranged from communities using theatre as an engagement platform in Nigeria to male-only community meetings in Pakistan. Close to 23,000 community engagement sessions have been conducted in the four sites. Community engagement sessions were structured in a context-specific manner to raise awareness and knowledge of hypertensive

disorders of pregnancy in the intervention cluster. They involved various stakeholders in the community including pregnant women, male decision makers, women of reproductive age, traditional birth attendants, health care providers and leaders who had been community, stakeholders and health care providers. These stakeholders came together to discuss and create meaningful, culturally and contextually appropriate sustainable change in aims to improve maternal health in their communities.

At the time of this report, outcome adjudication and data cleaning are near completion in all the three sites, and the trials are ready for preliminary analyses. The statistical analysis plan has been reviewed and approved by the CLIP Steering Committee. A list of the primary outcomes can be seen in the textbox on the next page. The primary outcome will be calculated by intention to treat. All statistical tests will be two-sided, with a significance level of  $< 0.05$  for the primary outcome, and  $< 0.01$  for secondary and other outcomes. Comparisons will be by means of risk ratios and mean differences with 95% confidence intervals for each site.

Furthermore, a process evaluation of the CLIP Trials is being undertaken to disentangle the various components of the intervention, and to understand the mechanisms of delivery of the intervention. A study of the implementation indicators provides important insight to the way the intervention interacts in the given context, and how to ensure the replicability or scalability of the intervention.

As we embark on the primary analysis of the CLIP Trials, it is important to acknowledge, and offer gratitude to, the tens of thousands women who participated, each of these women has allowed a generation of scientists a window into the journey of her pregnancy. The data from these women will help the scientific community answer critical questions and will serve the policy community to practice accountability. It is with this knowledge that we thank the women, and applaud the efforts of the study teams.

## Definition of the Primary Outcome

**Maternal death** (defined as the number of deaths during pregnancy or within 42 days of delivery (or the last postpartum contact day if contact not maintained to 42 days postpartum) / 1,000 identified pregnancies)

**Maternal morbidity** (defined as the number of women with one or more life-threatening complications of pregnancy during pregnancy or within 42 days of delivery or last postpartum contact day if contact not maintained to 42 days) / 1,000 identified pregnancies).

### Serious End-organ Complication of Pre-eclampsia

- Eclampsia: occurrence of generalised convulsions in the absence of epilepsy or another condition predisposing to convulsions
- Stroke: hemiparesis and/or blindness lasting greater than 48 hours
- Coma: prolonged unconsciousness  $\geq 12$  hours
- Antepartum haemorrhage: vaginal bleeding  $\geq 15$  mL with or without pain before the onset of labour
- Disseminated intravascular coagulation: abnormal bleeding from mucosa (mouth and/or ears)

### Other Major Causes of Maternal Mortality

- Obstetric sepsis: fever and one of: abdominal/uterine tenderness, foul smelling vaginal discharge/lochia, productive cough and shortness of breath, dysuria or flank pain, headache and neck stiffness.
- Vesicovaginal or rectovaginal fistula: continuous loss of urine and/or faeces after delivery

### Life-saving Interventions

- Cardiopulmonary resuscitation: a set of emergency procedures including chest compressions and lung ventilation applied in cardiac arrest victims
- Dialysis: haemodialysis and/or peritoneal dialysis
- Mechanical ventilation (other than for Caesarean delivery): intubation and ventilation not related to anaesthesia

- Blood transfusion:  $\geq 1$  unit of any type of blood product
- Interventions for major postpartum haemorrhage: brace sutures, external and internal uterine compression, anti-shock garment use, internal iliac artery ligation and/or hysterectomy with or without transfusion

**Perinatal & late neonatal death** (defined as stillbirth [ $\geq 20+0$  weeks and/or  $\geq 500$ g in weight], early neonatal mortality [d 0-7 of postnatal life] and late neonatal mortality [d 8-28 of postnatal life] / 1,000 identified pregnancies)

**Neonatal morbidity** (defined as occurrence of a primary neonatal morbidity during d 0-28 of postnatal life / 1,000 identified pregnancies).

- Feeding difficulty: Including inability to suckle normally or latch on to the mother's breast to feed even if the mother's milk is not let down
- Breathing difficulty: Including grunting and in-drawing of the abdomen under the ribs
- Seizure: Occurrence of any seizure event
- Lethargy: Baby not appearing normally wakeful after activities such as feeding or sleeping
- Coma: Not medically induced period of unconsciousness of any length
- Hypothermia: Cold to touch
- Umbilical cord infection: discharge from and redness around the umbilical stump
- Skin infection: Any appearance of abnormally red, black, swollen and blistered skin with pus
- Bleeding: From anywhere
- Jaundice: Yellow skin and eyes
- Central nervous system related morbidity: Abnormal amount of vomiting as defined by the parents or caregiver with bulging or sunken fontanelle

# CLIP Mozambique

**Site Investigators:** Esperança Sevene, Khátia Munguambe, Charfudin Sacoor

**Trainee:** Charfudin Sacoor (PhD student)

**Co-ordinator:** Anifa Vala

**Partner Institutions:** Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique ; Eduardo Mondlane University, Maputo, Mozambique

The CLIP Definitive Trial in Mozambique took place in two provinces: Gaza and Maputo, and was the only of the CLIP Trials to not have a Pilot phase. Despite the challenges that the lack of pilot may have offered, the trial made great strides and effectively ended recruitment on February 24, 2017 after recruiting over 15,000 pregnancies. There were over 18,000 participants engaged in over 4,200 community engagement sessions.

The community engagement strategy was led by the CLIP community engagement team (mobilizers, activists, and community liaison officer), supported by APEs, health facility nurses, community leaders. Sixteen nurses did health talks with key messages about pre-eclampsia and eclampsia at the health facilities. Five community members (activists) were trained to pass on messages



house to house and in group sessions. Three mobilisers held group sessions in the community. Community leaders helped to organise large community meetings with the community liaison officer.

By engaging the communities at various levels, the CLIP Team at CISM was able to facilitate an innovative solution to increase access to care. During the Feasibility Study, it became apparent that the delays in women seeking emergency obstetric care were not only due to a lack of transport, long distances and complex decision-making dynamics; a lack of money for transport and poor transport infrastructure were identified as contributing factors. A needs assessment was conducted to inform the design of a transport scheme that would meet the needs of the community. The CLIP Trial provided seed funds for the set-up of the transport schemes. Following the needs assessment study, nine neighbourhoods pioneered to contribute money to the seed fund.

By the end of the trial, there were thirteen neighbourhoods actively using the transport scheme. Furthermore, eighteen people have used this fund to access care, and the majority (fourteen) beneficiaries were pregnant or postpartum women.

*“The participant said she was very pleased with the study because she had already received an APE visit.”*

—A study member reflecting on the information discussed at the community engagement session

*“I felt very good about being transported to the hospital by the transport scheme when I needed and I would like to encourage the community to continue contributing the money for the funds because it helps people a lot. I hope this project continues to help more people. I’m very grateful to the management committee who called the transporter and if it were not for this I would have given birth at home. I will continue to contribute to the fund because I saw the importance of it”.*

—A pregnant woman who benefitted from the transport plan discusses her experience at a community engagement session

ABOVE RIGHT: A pregnant woman being assisted by the APE (in green, right) after a referral to higher care facility in Mozambique.

## Stories from the Field

### Meet Ana Lisa, a CLIP Study Mobiliser

I am Ana Lisa, I am a study mobiliser, working with the CLIP Trial. My tasks include conducting community engagement activities and supervising health talks conducted by community health workers and primary health centre nurses in Gaza Province. During my supervision activities at the Licilo health facility in Chissano, I came across a nurse assisting a pregnant woman with convulsions in the maternity ward. She was trying to stabilize the woman with medication but the woman could not swallow the pills. The convulsions became stronger; her tongue was out, with her teeth clenched so the nurse put cotton in her mouth to prevent her from getting hurt. The nurse also tried to put her on a drip but because of the convulsions the needle pulled away and the woman continued to convulse. An ambulance to take the woman to Xai-Xai provincial hospital was requested but it was taking too long to arrive, so I offered to take the woman with the CISM car, to which the nurse accepted and gave her thanks. Normally, this woman would have been referred to the next level health facility (in this case Macia Health Centre), but the nurse decided that she should be referred directly to Xai-Xai provincial hospital because she was in a critical condition.

The nurse and I, along with two of the woman's family members took the woman to Xai-Xai provincial hospital. During the trip, the convulsions continued and she began to haemorrhage. The nurse continued her efforts to provide oral medication until we arrived at Xai-Xai. When we arrived, the woman was immediately taken to the observation room, and shortly after, the nurse informed us that she would undergo an emergency Caesarean section. A few days later, I was informed that the Caesarean section had been successful. Although the woman was unconscious for a week and the baby had to stay in an incubator,

they were both well enough to be discharged two weeks later.

I was very happy to have contributed to saving the life of a mother at risk who managed to give birth to a live baby (although unfortunately the baby died two months later). What happened with this woman is a practical example of everything I have learnt, and have been talking about during my mobilisation activities. In particular, it was a practical example of the risks, presentation, management and consequences of untreated eclampsia as well as the importance of being assisted by skilled health professionals and the importance of prompt referrals to the appropriate level of care. Witnessing how this woman and her family suffered made me realize the importance of interventions such as CLIP and the need to roll them out beyond the study. I felt like a heroine when I received news that the woman and her baby were doing well. I hope this project does not stop here, but that it is implemented in other communities of our country and the world to help save more lives.

### A Community Success Story

My name is Dulce; I am a research nurse with the CLIP study in Manhiça. My role as study nurse includes training and supervising the APEs and primary health centre nurses' activities in the intervention clusters in Maputo and Gaza Provinces.

On my way back to Manhiça, after performing supervisory visits in Chissano (Gaza Province), I received a call from an APE asking me to come back to help transport a pregnant woman whose POM visit recommended urgent referral due to hypertension (210/190 mmHg). The APE had already administered three tablets of methyldopa and two ampoules of magnesium sulphate. When I arrived, the woman was doing her domestic activities and I was amazed because I was expecting to see a sick woman. I spoke with the woman, who claimed to be feeling good. I then

measured her blood pressure again and found that it was getting even higher (240/200 mmHg). I observed her feet and found no oedema. I explained to her that although she felt fine, she was very sick and needed to go with us to the health facility. She refused, saying that she was feeling well. Her mother-in-law also refused, as she saw no reason for her to go to the health facility. I explained again to the mother-in-law that although she felt good, the POM said that she was not well and had to go to the hospital immediately, and that if she stayed at home, something more serious could happen. I told her that I was a nurse and together with the APE and the hospital we are fighting to prevent various diseases, and our results (meaning the POM readings) were recommending that she should go to the health facility to be observed. The family eventually accepted, and we took the woman to the Chissano health centre. When we arrived at the health facility, I explained everything to the nurse and she measured the woman's blood pressure again and found that it was increasing. The

nurse administered magnesium sulphate and asked for an ambulance from the provincial hospital. Days later, we received news that on that same day, the woman had a healthy baby via cesarean delivery. One week later, the woman was discharged and returned home. After that her relatives went to the APE's house to thank him and the nurse for insisting on taking the woman to the health facility.

This work that we are doing in the communities is very important. It is beneficial to have APEs from the communities as many do not have access to health care and we know that pregnant women need a lot of care. If we had not persuaded this woman to go to the health facility on time, she could have died and no one would have been able to explain the cause of her death. I am very happy to know that I helped save someone's life and I would like it if this project or CISM looked for other initiatives like these to help take care of the health of these communities.

## CLIP India Trial

**Site Investigators:** Mrutunjaya Bellad, Ashalata Mallapur, Shivaprasad Goudar

**Co-ordinators:** Umesh Charantimath, Geetanjali Katageri

**Partner Institutions:** Jawaharlal Nehru Medical College, Belgaum, India; S.Nijalingappa Medical College and Hanagal Shree Kumareswar Hospital and Research Centre Bagalkot, India

The CLIP India Trial was undertaken in two districts in the state of Karnataka: Belgaum ('Belagavi') and Bagalkot. The CLIP India Trial was the first to finish recruitment at the end of October 2016. Over 14,700 pregnancies were enrolled over three years and close to 65,000 CLIP visits were done. More than 1,350 community engagement sessions were conducted, and almost 22,000 women of reproductive age were engaged.

Another significant accomplishment of the India team has been the remarkable rate of follow-up of women in the trial. This success may be attributed to the Maternal and Newborn Child Health Registry (MNH Registry),

a prospective data collection registry. The negligible loss to follow-up was similar in the CLIP India baseline assessment, now published and open-access in PLoS One (see abstract below).

The MNH Registry, coupled with community engagement resulted in early identification of pregnancies -as early as eight weeks of gestation in some cases. Early identification of pregnancies will facilitate the CLIP India Trial to provide reliable information on the rates of miscarriages in these communities.

Over the three-year trial period, 123 community health care providers (ASHAs and ANMs) served as

the frontline providers and mobilisers of the CLIP intervention. The ASHA (Accredited Social Health Activists) have proven themselves to be the pillars of primary care strengthening in their communities. A special permission from the Indian Council of Medical Research, the Government of India and Ministry of Health and Family Welfare to allow the ASHA workers to check the blood pressure for the CLIP Trial, awarded the ASHA workers with a clinical role, a departure from their health promotion and vaccination activities. The ASHAs showed proficiency in understanding how to operate

the blood pressure device, and served as educators by informing their communities about the importance of blood pressure measurement. By the end of the trial, the team reported that the ASHAs were called as “BP doctor(s)” in the community—and ASHAs reported that their status was elevated in their community.

The CLIP India Trial also saw the vertical integration of CLIP referral into the health system. The women in Belgaum received a yellow referral card, which enabled them to present to the labour ward directly without having to register elsewhere in the hospital. In case of

## Abstract

Existing vital health statistics registries in India have been unable to provide reliable estimates of maternal and newborn mortality and morbidity, and region-specific health estimates are essential to the planning and monitoring of health interventions. This study was designed to assess baseline rates as the precursor to a community-based cluster randomized control trial (cRCT)—Community Level Interventions for Pre-eclampsia (CLIP) Trial (NCT01911494; CTRI/2014/01/004352). The objective was to describe baseline demographics and health outcomes prior to initiation of the CLIP trial and to improve knowledge of population-level health, in particular of maternal and neonatal outcomes related to hypertensive disorders of pregnancy, in northern districts the state of Karnataka, India. The prospective population-based survey was conducted in eight clusters in Belgaum and Bagalkot districts in Karnataka State from 2013–2014. Data collection was undertaken by adapting the Maternal and Newborn Health registry platform, developed by the Global Network for Women’s and Child Health Studies. Descriptive statistics were completed using SAS and R. During the period of 2013–2014, prospective data was collected on 5,469 pregnant women with an average age of 23.2 (+/-3.3) years. Delivery outcomes were collected from 5,448 completed pregnancies. A majority of the women reported institutional deliveries

(96.0%), largely attended by skilled birth attendants. The maternal mortality ratio of 103 (per 100,000 livebirths) was observed during this study, neonatal mortality ratio was 25 per 1,000 livebirths, and perinatal mortality ratio was 50 per 1,000 livebirths. Despite a high number of institutional deliveries, rates of stillbirth were 2.86%. Early enrollment and close follow-up and monitoring procedures established by the Maternal and Newborn Health registry allowed for negligible lost to follow-up. This population-level study provides regional rates of maternal and newborn health in Belgaum and Bagalkot in Karnataka over 2013–14. The mortality ratios and morbidity information can be used in planning interventions and monitoring indicators of effectiveness to inform policy and practice. Comprehensive regional epidemiologic data, such as that provided here, is essential to gauge improvements and challenges in maternal health, as well as track disparities found in rural areas.

The CLIP India Trial baseline study has been published in *PLoS One*:

- Bellad MB, Vidler M, Honnungar NV, Mallapur A, Ramadurg U, Charanthimath U, Katageri G, et al. Maternal and Newborn Health in Karnataka State, India: The Community Level Interventions for Pre-Eclampsia (CLIP) Trial’s Baseline Study Results. *PLoS One*. 2017 Jan 20;12(1):e0166623.

POM-triggered referrals, the women could call a 24 hour helpline (set up by the site study team). The helpline was manned by designated personnel to sort logistic issues and to advise on the nearest ambulance or other transport. The helpline personnel also alerted the nurses, residents and staff of the transfer and of the particulars of the patient so that they may be prepared. In Bagalkot, the women receive a blue referral card for admission to

the HSK Hospital. The department of OBGYN at HSK Hospital had a separate entrance which allows for ease of navigation during the referral processes. In both the sites, the logistics of the referrals were co-ordinated by the central research team through a messaging application (WhatsApp). This referral process, strengthened by the use of text messaging helped develop a more responsive referral chain at all levels.

## Stories from the Field

### **A Story of Resilience: An Asha Worker Who Lost Her Leg but Found the Will to Carry On Conducting CLIP Visits**

Suvarna Siddhapur, a community health worker (ASHA) in the CLIP India Trial in Sutagundar, Bagalkot, had an unfortunate train accident in October 2015. To save her life, the doctors performed an amputation of her left lower limb. As a result, she could no longer carry out her duties as an ASHA worker, which involves conducting antenatal and postnatal home-based visits, health promotion activities and community mobilisation. Subsequently, Suvarna's daughter volunteered to join the CLIP team to continue follow-up of the women that Suvarna was managing. Her daughter received CLIP training and began conducting home visits and monitoring blood pressure.

Six months after her accident, Suvarna expressed an interest to return to her role as an ASHA in the CLIP Trial. Now with the help of an artificial limb, Suvarna returned to work. However, she did not limit herself to conducting local CLIP visits, but also travelled outside



her village to conduct CLIP visits for women who migrated to their maternal homes. She travelled by two-wheeler with her son, or by public transport. Suvarna is a testament to the resilience and determination of the community health workers, and she has been a great asset to her community as well as the CLIP India Trial. Reflecting on her experience, Suvarna expresses gratitude to the CLIP India Trial; she believes that the responsibility entrusted to her fuelled her determination and drive to overcome her physical limitations.

## CLIP Pakistan Trial

**Principal Investigators:** Rahat Qureshi, Zulfiqar Bhutta

**Co-ordinators:** Sana Sheikh, Zahra Hoodbhoy

**Partner Institution:** Aga Khan University, Karachi, Pakistan

The CLIP Trial in Hyderabad and Matiatri districts in Sindh province, Pakistan ended on 31 December 2016; recruiting over 39,000 pregnancies, the CLIP Pakistan Trial is the largest of the three CLIP Trials. The CLIP Pakistan Trial was the only one of the CLIP Trials to move from paper-based data collection in the one-year Pilot Trial to electronic data capture in the two-year Definitive Trial. Electronic data capture allowed for robust data collection and facilitated rapid data monitoring.

As the reporting of medical interventions may vary among populations with varying levels of medical literacy, the CLIP Pakistan team championed a thorough outcome adjudication process to ensure rigour in the quality of reported data. Each reported outcome triggered a review by a committee of clinicians, whereby a medical case

history of the patient was reviewed. This prudent review also aided the iterative training of surveillance workers to ensure that the communities understood the questions.

The seemingly formidable task of co-ordinating multiple surveillance activities for each recruited pregnancy, careful data management, and a clinical review of each outcome in this large cohort of women speaks volumes to the commitment of the study team at Aga Khan University.

Over 58,000 visits were conducted using POM, and over 17,000 community engagement sessions were conducted with members of the community. Lady Health Workers (LHWs), the community health workers in Pakistan, provided CLIP visits and conducted one-on-one counselling sessions with pregnant women.

### Stories from the Field

#### A Story of Appreciation from Masu Bhurgri, Hyderabad

After a successful conclusion of the CLIP Trial, the LHWs and their supervisor from a union council in Hyderabad organised an appreciation lunch for the field research team.

The LHWs formally thanked the CLIP team for increasing their knowledge and skills regarding pre-eclampsia and appropriate treatment. Reflecting on their experience, the LHWs stated that they felt empowered to impart this knowledge to women in their community. The lady health supervisor (LHS) mentioned that “pregnant women of our villages were happy to receive information provided through CLIP and to have their blood pressure measured in their homes”. The LHWs also appreciated the co-ordination and facilitation provided by the CLIP team to ensure



that field activities were performed efficiently. The CLIP team took the opportunity to thank the LHWs and LHS for cooperating with them and for arranging this special occasion.

This was a proud moment indeed for the entire CLIP Pakistan Team!

ABOVE RIGHT: Members of the CLIP surveillance team pose for picture at an appreciation event organised by lady health workers in Masu Bhurgri.

A notable achievement of the LHWs has been their rapid adaptation of new technology. This involved the operation of mobile health device (with the PIERS on the Move risk assessment application), in conjunction with a portable pulse oximeter, and a digital blood pressure device. Throughout the life of the trial, the LHWs have demonstrated remarkable proficiency with these technologies.

The communities have also shown responsiveness to the community engagement activities aimed at raising

awareness about hypertensive disorders of pregnancy. During the CLIP Feasibility Study, a reported barrier to the acceptance of referral was the lack of permission from the head of the household. By targetting key stakeholders, namely the husbands and male stakeholders in the community, the study team facilitated prior permissions in case of obstetric emergencies or referrals to the facility. The rate of acceptance of urgent referral is observed to have steadily increased over time.

## CLIP Nigeria Trial

**Site Investigators:** Olalekan Adetoro, John Obafemi Sotunsa, Olukayode Dada

**Co-ordinator:** Akinmade Adepoju

**Partner Institution:** Center for Research in Reproductive Health, Olabisi Onabanjo University Teaching Hospital, Ogun, Nigeria

The CLIP Nigeria Trial was designed to be undertaken in Ogun State as a pilot and then definitive cluster randomized control trial. However, challenges with data collection and data entry prompted the decision to change the research design in Nigeria to one of process evaluation. To complement the effectiveness trials in Mozambique, India, and Pakistan, the process evaluation in Nigeria will serve to assure policy makers in Nigeria that the CLIP intervention can be undertaken successfully and is supported by both the community at large and health workers at various levels. The process evaluation in Nigeria will involve data collected electronically on the POM mobile application, as well as that from community engagement and other monitoring logs. The CLIP Nigeria process evaluation framework was published in BMC Health Services Research (see textbox).

Members of the CLIP Nigeria team were invited to present two abstracts from the process evaluation of CLIP Nigeria Trial in West African Health Organisation (WAHO) Conference in Abidjan, Côte d'Ivoire from 26-28 October. This forum represents members from fifteen countries and brings together hundreds of senior officials from ministries of health; regional health researchers and experts; non-profit organisations; and partners in the



public and private sectors. Notable partners of the forum included: USAID, KFW, WHO, UNFPA, UNICEF, African Union, JHPEIGO and Pathfinder International. The theme this year was “Promoting Innovations in Reproductive, Maternal, Newborn, Child and Adolescent Health related Sustainable Development Goals.”

Two oral presentations were presented on the CLIP Nigeria Trial:

- “The cost of implementing a mobile health intervention for pre-eclampsia in Ogun State, Nigeria” by Akinmade Adepoju, Ibiezugbe OO, Drebit S, Khowaja AR, Dada

## Abstract

### Background

Despite increased investment in community-level maternal health interventions, process evaluations of such interventions are uncommon, and can be instrumental in understanding mediating factors leading to outcomes. In Nigeria, where an unacceptably number of maternal deaths occur (maternal mortality ratio of 814/100,000 livebirths), the Community Level Interventions for Pre-eclampsia (CLIP) study (NCT01911494) aimed to reduce maternal and neonatal mortality and morbidity with a complex intervention of five interrelated components. Building from previous frameworks, we illustrate a methodology to evaluate implementation processes of the complex CLIP intervention, assess mechanisms of impact and identify emerging unintended causal pathways.

### Methods

The study was conducted from 2013–2016 in five Local Government Areas in Ogun State, Nigeria. A six-step approach was developed to evaluate key constructs of context (external factors related to intervention), implementation (fidelity, dose, reach, and adaption) and mechanisms of impact (unintended outcomes and mediating pathways). The steps are: 1) describing the intervention by a logic model, 2) defining acceptable delivery, 3) formulating questions, 4) determining

methodology, 5) planning resources in context, lastly, step 6) finalising the plan in consideration with relevant stakeholders.

### Results

Quantitative data were collected from 32,785 antenatal and postnatal visits at the primary health care level, from 66 community engagement sessions, training assessments of community health workers, and standard health facility questionnaires. Forty-three focus group discussions, 38 in-depth interviews, and 23 structured observations were conducted to capture qualitative data. A total of 103 community engagement reports and 182 suspected pre-eclampsia case reports were purposively collected. Timing of data collection was staggered to understand feedback mechanisms that may have resulted from the delivery of the intervention. Data will be analysed using R and NVivo. Diffusions of innovations and realist evaluation theories will underpin analysis of the interaction between context, mechanisms and outcomes.

### Conclusion

This comprehensive approach can serve as a guide for researchers and policy makers to plan the evaluation of similar complex health interventions in resource-constrained settings, and to aid in measuring ‘effectiveness’ of interventions and not just ‘efficacy’.

OA, Kariya C, Ikpeama G, Adetoro OO, Sotunsa JO, Jaiyesimi E, Bhutta ZA, Magee LA, von Dadelszen P and the CLIP Nigeria Working Group

- “The ability of community-based health workers to triage pre-eclampsia by use of an mHealth platform in Ogun State, Nigeria: An analysis of 8,791 pregnancies” by Adebayo Akadri, Drebit S, Adepoju AA, Payne B, Dunsmuir D, Jaiyesimi E, Vidler M, Sotunsa JO, Ibiezugbe OO, Lui M, Li J, Adetoro OO, von Dadelszen

P, Dada OA, Oladapo OT, Ansermino M, Magee L, Bhutta Z, Soyinka O and the CLIP Nigeria Working Group

The presentations were well-received and cultivated lively discussions from the audience, particularly on the issue of task-sharing and the cost-effectiveness of the CLIP Nigeria intervention. Participation at the meeting provided the CLIP Nigeria team members a valuable opportunity to interact and network with other researchers, including key officials from the Federal Ministry of Health, Nigeria.

## Stories from the Field

### Experiences of Pre-eclampsia and Eclampsia in Ogun State

On January 21, 2015, in a rural district of Ilaro in Southwest Nigeria, Achebe\* was rushed to the primary health centre (PHC). Achebe typically went to the PHC for regular antenatal care as part of the CLIP Trial. Here, she was assessed by community health extension workers using the PIERS on the Move (POM) mobile health application, which serves as a risk stratification tool, and the CRADLE blood pressure device. On this day, Achebe presented with severe hypertension (177/135mmHg), along with unconsciousness and seizures. The field officer on site was told that she had previously convulsed at home, was resuscitated, and had a wooden stick inserted in her mouth and had her legs set on fire. As well, the field officer was told that in a previous visit to the PHC, she was unable to get a blood pressure reading due to the fitting of the blood pressure cuff.

During this assessment, the POM device recommended an urgent referral to the hospital, and treatment with MgSO<sub>4</sub>. The field officer directed and followed them to Hosanna Hospital, where she again convulsed and

\* Name changed to protect privacy

was treated with MgSO<sub>4</sub>. She underwent a Caesarean section and thankfully, both mother and child survived.

Achebe remained in the hospital until the 27<sup>th</sup> of January. The doctor said she could be discharged the same day, unless she was unable to pay her medical bills. The cost of her care totalled 128,000 Naira (\$669 USD), but her husband was only able to afford 100,000 (\$523 USD). After a day of discussion, it was decided that 28,000 Naira (\$89 USD) would be paid by a fund for obstetric emergencies managed by the CLIP team in Nigeria, and the remaining 100,000 by Achebe's husband. She was discharged normotensive on January 28.

Four weeks later, Achebe participated in a follow-up interview with both field officer and supervisor. Here, she expressed gratitude for God, the field officer, and the CLIP project for their effort in saving lives of mothers and babies. "If not for God or the field officer," expressed Achebe, "I would not know where I am now."

Achebe is now part of a group of pre-eclampsia survivors who educate pregnant women and community members on the warning signs and symptoms of hypertensive disorders of pregnancy.

- Sharma S, Adetoro OA, Vidler M, Drebit S, Payne BA, Akeju DO, Adepoju A, Jay E, Sotunsa J, Bhutta ZA, Magee LA, von Dadelszen P, Dada O. A process evaluation plan for assessing a complex community-based maternal health intervention in Ogun State, Nigeria. *BMC Health Serv Res.* 2017;17(1):238.

## Year 8 Deliverables

The main deliverable for the CLIP Trials over the next year will be analysis and publication of the studies in a high-impact journal. In addition to determining whether the CLIP intervention is effective in reducing all-cause related morbidity and mortality by 20%, the CLIP Trials

have a unique opportunity to inform the scientific and policy community of the prevalence of life-threatening morbidities in women and babies. The data on blood pressure, gathered using the validated CRADLE device, may provide an understanding of the epidemiology of the hypertensive disorders of pregnancy in: Nigeria, Mozambique, Pakistan and India.

A process evaluation is being conducted in parallel to understand the 'how' and the 'why' of the CLIP Trials. This will play a key role in dis-entangling the complex CLIP intervention and the interaction of various components with the health system.

## Presentations

Members of the Mozambique team presented findings from the CLIP Mozambique health facility assessments and the community transportation plan at the American Society of Tropical Medicine and Hygiene symposium from 13-17 November in Atlanta, United States:

- “Health facility preparedness for management of obstetric emergencies in South Mozambique” by Anifa Valá, Salésio Macuacua, Raquel Catalão, Helena Boene, Marianne Vidler, Orvalho Augusto, Eusébio Macete, Mohsin Sidat, Clara Menéndez, Khátia Munguambe, Peter Von Dadelszen, and Esperança Sevene – Poster
- “A Community transport strategy to address emergency obstetric care needs in Maputo and Gaza provinces, Mozambique” by Felizarda E. Nhacolo, Helena Boene, Sharla Drebit, Marianne Vidler, Anifa Valá, Eusebio Macete, Peter Von Dadelszen, Esperança Sevene, and Khátia Munguambe – Poster

Marianne Vidler presented at the Qualitative Health Conference, in November, in Kelowna, Canada in November 2016:

- “Women’s Perceptions of the Hypertensive Disorders of Pregnancy in Nigeria, Mozambique, Pakistan, and India: A Qualitative Evidence Synthesis of Primary Data from the Community-Level Interventions for Pre-Eclampsia (CLIP) Feasibility Study”

Felizarda Nhacolo presented at the Eduardo Mondlane University Scientific Conference, September 27-28, 2016:

- “A Community transport strategy to address emergency obstetric care needs in Maputo and Gaza provinces, Mozambique” by Felizarda E. Nhacolo, Helena Boene, Sharla Drebit, Marianne Vidler, Anifa Valá, Eusebio Macete, Peter Von Dadelszen, Esperança Sevene, and Khátia Munguambe – Oral presentation

Umesh Ramadurg from the CLIP India team presented the CLIP India baseline study results at 61st Annual National Indian Public Health Association’s Conference, February 24-26, 2017:

- “Maternal and Newborn Health in Karnataka State, India: The Community Level Interventions for Pre-Eclampsia (CLIP) Trial’s Baseline Study Results” by

Mrutunjaya Bellad, Marianne Vidler, NV Honnugar, Ashalata Mallapur, Umesh Ramdurg, Umesh Charantimath et al. – Oral presentation

Ebunolwa Jaiyesimi presented at the West African College of Physicians Annual General and Scientific Meeting in Nigeria, July 18-22 2016:

- “Process of Task Shifting: Community Health Care Workers Identification and Management of Preeclampsia in Ogun-State Nigeria” by Ebunolwa Jaiyesimi, Sharla Drebit, Akinmade Adepoju, David O Akeju, Marianne Vilder, O Adejumo et al.- Oral presentation

## Publications

- Sharma S, Adetoro OO, Vidler M, Drebit S, Payne BA, Akeju DO, Adepoju A, Jaiyesimi E, Sotunsa J, Bhutta ZA, Magee LA. A process evaluation plan for assessing a complex community-based maternal health intervention in Ogun State, Nigeria. *BMC Health Serv Res.* 2017;17(1):238.
- Bellad MB, Vidler M, Honnungar NV, Mallapur A, Ramadurg U, Charanthimath U, Katageri G, et al. Maternal and newborn health in Karnataka State, India: the Community Level Interventions for Pre-eclampsia (CLIP) Trial’s baseline study results. *PLoS One.* 2017;12(1).
- Qureshi R, Sheikh S, Khowaja A, Salam R, Vidler M, Sawchuck D, von Dadelszen P, Zaidi S, Bhutta Z, and the CLIP working group. Health care provider knowledge and routine management of pre-eclampsia in Pakistan. *Reprod Health.* 2016;13(2):107-113.
- Akeju D, Vidler M, Sotunsa J, Osiberu M, Orenuga E, Oladapo O, Adepoju A, Qureshi R, Sawchuck D, Adetoro O, von Dadelszen P, Dada O, and the CLIP Nigeria Feasibility Working Group. Human resource constraints and the prospect of task-sharing among community health workers for the detection of early signs of pre-eclampsia in Ogun State, Nigeria. *Reprod Health.* 2016;13(2):115-122.
- Firoz T, Vidler M, Makanga PT, Boene H, Chiaú R, Sevene E, Magee LA, von Dadelszen P, Munguambe K, and the CLIP Working Group. Community



perspectives on the determinants of maternal health in rural southern Mozambique: a qualitative study. *Reprod Health*. 2016;13(2):123-131.

- Sotunsa J, Vidler M, Akeju D, Osiberu M, Orenuga E, Oladapo O, Adepoju A, Qureshi R, Sawchuck D, Adetoro O, von Dadelszen P, Dada O, and the CLIP Nigeria Feasibility Working Group. Community health workers' knowledge and practice in relation to pre-eclampsia in Ogun State, Nigeria: an essential bridge to maternal survival. *Reprod Health*. 2016;13(2):133-139.
- Ramadurg U, Vidler M, Charanthimath U, Katageri G, Bellad M, Mallapur A, Goudar S, Bannale S, Karadiguddi C, Sawchuck D, Qureshi R, von Dadelszen P, Derman



R, and the Community Level Interventions for Pre-eclampsia (CLIP) India Feasibility Working Group. Community health worker knowledge and management of pre-eclampsia in rural Karnataka State, India. *Reprod Health*. 2016;13(2):141-148.

- Boene H, Vidler M, Augusto O, Sidat M, Macete E, Menéndez C, Sawchuck D, Qureshi R, von Dadelszen P, Munguambe K, Sevens E, and the CLIP Feasibility Working Group. Community health worker knowledge and management of pre-eclampsia in southern Mozambique. *Reprod Health*. 2016;13(2):149-162.

# A Randomised Controlled Trial of Sildenafil Therapy in Dismal Prognosis Early-Onset Intrauterine Growth Restriction (STRIDER) Trials

**Principal Investigators:** Katie Groom, Peter von Dadelszen, Kenneth Lim, Laura Magee, Sayrin Lalji, Louise Kenny, Wessel Ganzevoort, Zarko Alfirevic

**Funding:** Health Research Council New Zealand Project Grant, Nurture Foundation Grant (Neonatal Sub-study); Canadian Institutes of Health Research (CIHR); Health Research Board Health Research Awards (HRA); Netherlands Organisation for Health Research and Development (ZonMW); Medical Research Council (MRC) National Institute for Health Research (NIHR)

## Overview

The STRIDER randomised controlled trials are designed to determine whether maternal treatment with oral sildenafil citrate improves perinatal outcomes in pregnancies complicated by severe early-onset IUGR without increasing risks to the mother.

The STRIDER International Consortium Working Group is currently in the process of finalising the meta-analysis plan. The working group has also registered the protocol with PROSPERO.

STRIDER Consortium Trials: STRIDER UK has completed recruitment, 135 participants recruited, and they are in process of data analysis. STRIDER NZAus has also completed recruitment, 122 participants recruited, and their last participant is still on intervention. Dutch STRIDER is progressing well and has recruited 137 out of 354 participants so far. STRIDER Ireland is in the process of receiving final ethics approval following the successful formulation of an umbrella Data Safety Monitoring Board. Detailed information related to STRIDER Consortium trials can be viewed at <https://pre-empt.bcchr.ca/STRIDERConsortium>.

## STRIDER Canada

We are pleased to announce that the STRIDER Canada has successfully randomised its first active study participant. The study investigators are confident that 2017 will be a strong recruitment period. The iSTAR randomisation platform which was developed at the University of British

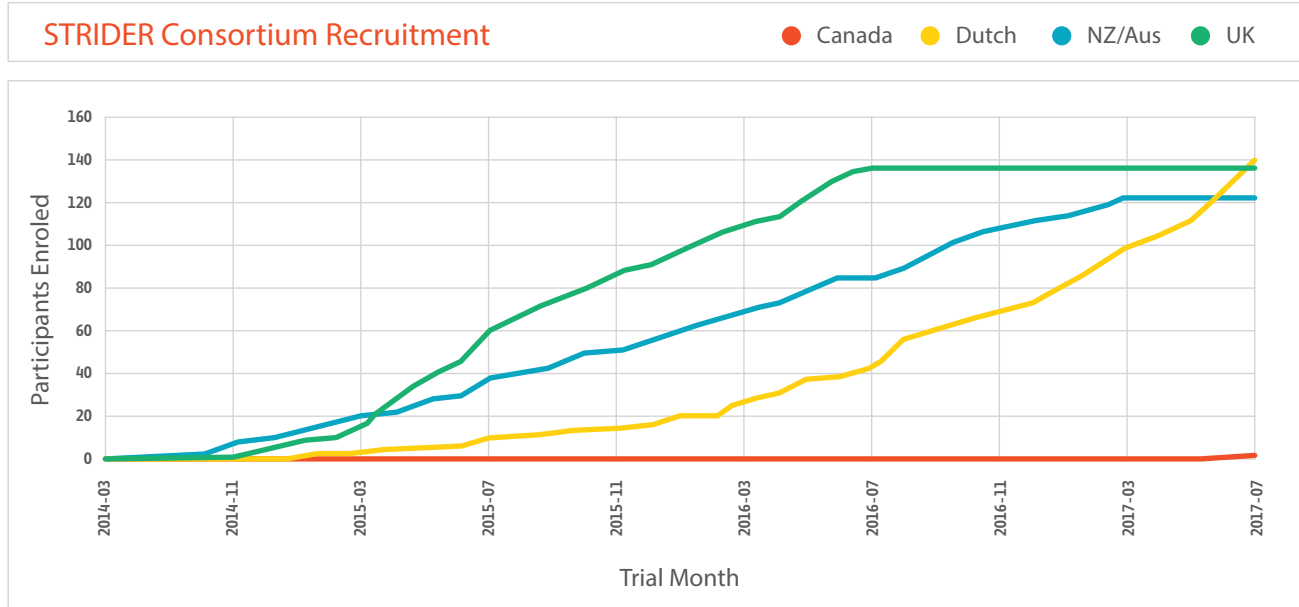


Columbia (UBC) and BC Children's Hospital Research Institute (BCCHR) has been very well-received at all of the active sites and will continue to garner awareness as the other sites across Canada become activated. The STRIDER Canada Coordinating Centre (SCC) will continue to focus on activating the remaining centres in Canada that are in

ABOVE RIGHT: Alere Triage meter and cartridge.

the midst of obtaining local REB approval and finalizing contract negotiations. The awareness and interest surrounding the trial continues to be high and there is an abundance of support from many health care professionals

at each respective study site. 2017 will continue to be a banner year for the STRIDER Canada trial. Detailed information related to STRIDER RCTs can be viewed <https://pre-empt.bcchr.ca/STRIDERCanda>.



# Control of Hypertension in Pregnancy Study (CHIPS) Trial

**Principal Investigator:** Laura Magee

**Funding:** Canadian Institutes of Health Research

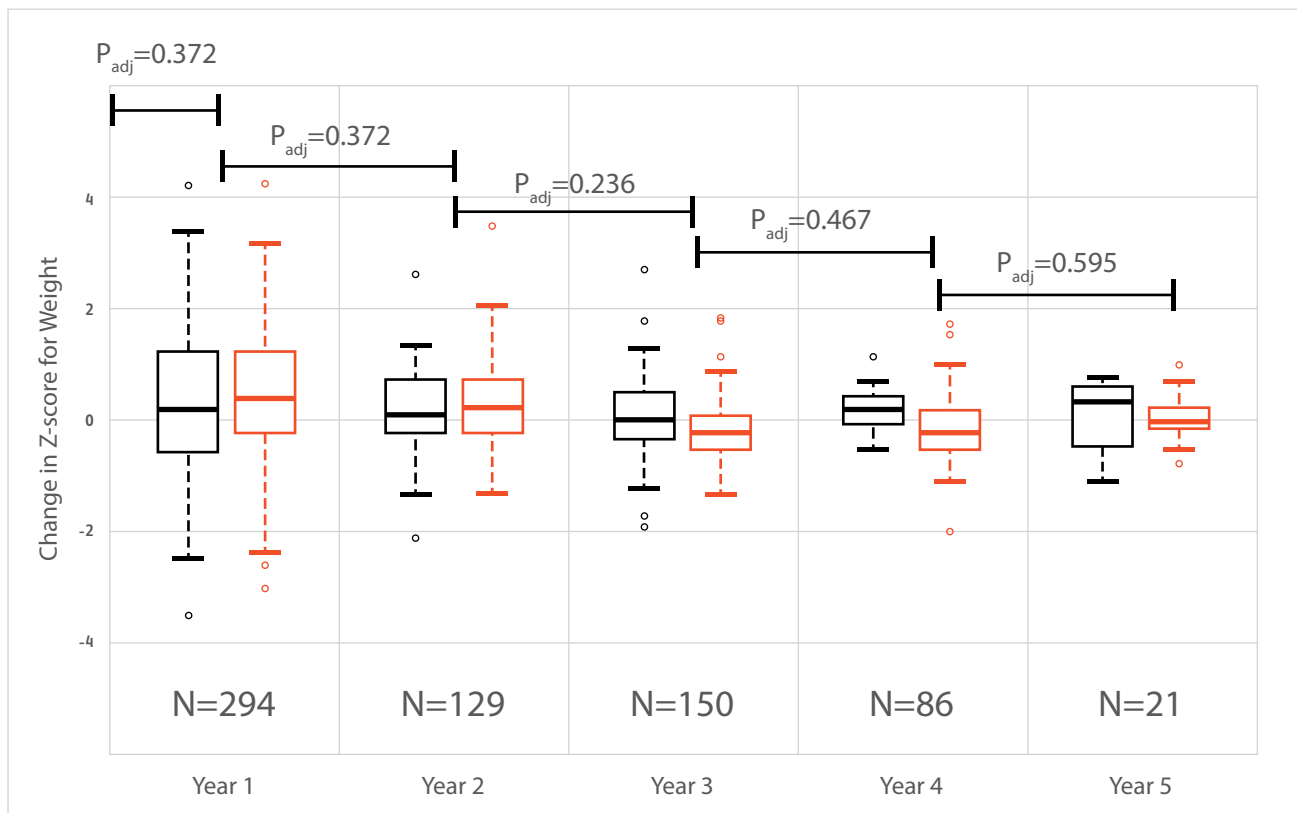
## Overview

The CHIPS Trial (ISRCTN 71416914, <https://pre-empt.bcchr.ca/treatment/chips>, 2015) provided evidence that antihypertensive treatment of non-severe hypertension in pregnancy is of benefit to the mother, without associated perinatal risk. Since the 2015-6 PRE-EMPT Annual Report, CHIPS-Child (the CHIPS follow-up study) has been

completed, and further secondary analyses of CHIPS data have been conducted.

CHIPS-Child investigated the potential developmental programming effects of maternal blood pressure (BP) control in pregnancy. Out of the 59/94 participating CHIPS sites, CHIPS follow-up (500/683, 73.2%) was extended to 12±2 months corrected post-gestational age. The primary outcome, 'change in z-score for weight' between birth and 12±2mos, did not differ between less tight' (vs. 'tight')

### Change in Z-score for Weight by Year Compared with Year Before



ABOVE: Postnatal growth rate relative to year before in 'less tight' (black) and 'tight' (red) BP control groups.

control [-0.26 (-0.53, +0.01);  $p=0.14$ ,  $p_{\text{adjusted}}=0.06$ ]. Also, there was no difference in annual postnatal growth rate from birth to 5 years in 'less tight' (vs. 'tight') control, despite the impression that postnatal growth rate in 'less tight' may have been slower until 2 years and then more rapid from 3-5 years. The results provide no compelling evidence for developmental programming of growth. Clinicians should look to the clinical findings of CHIPS to guide practice.

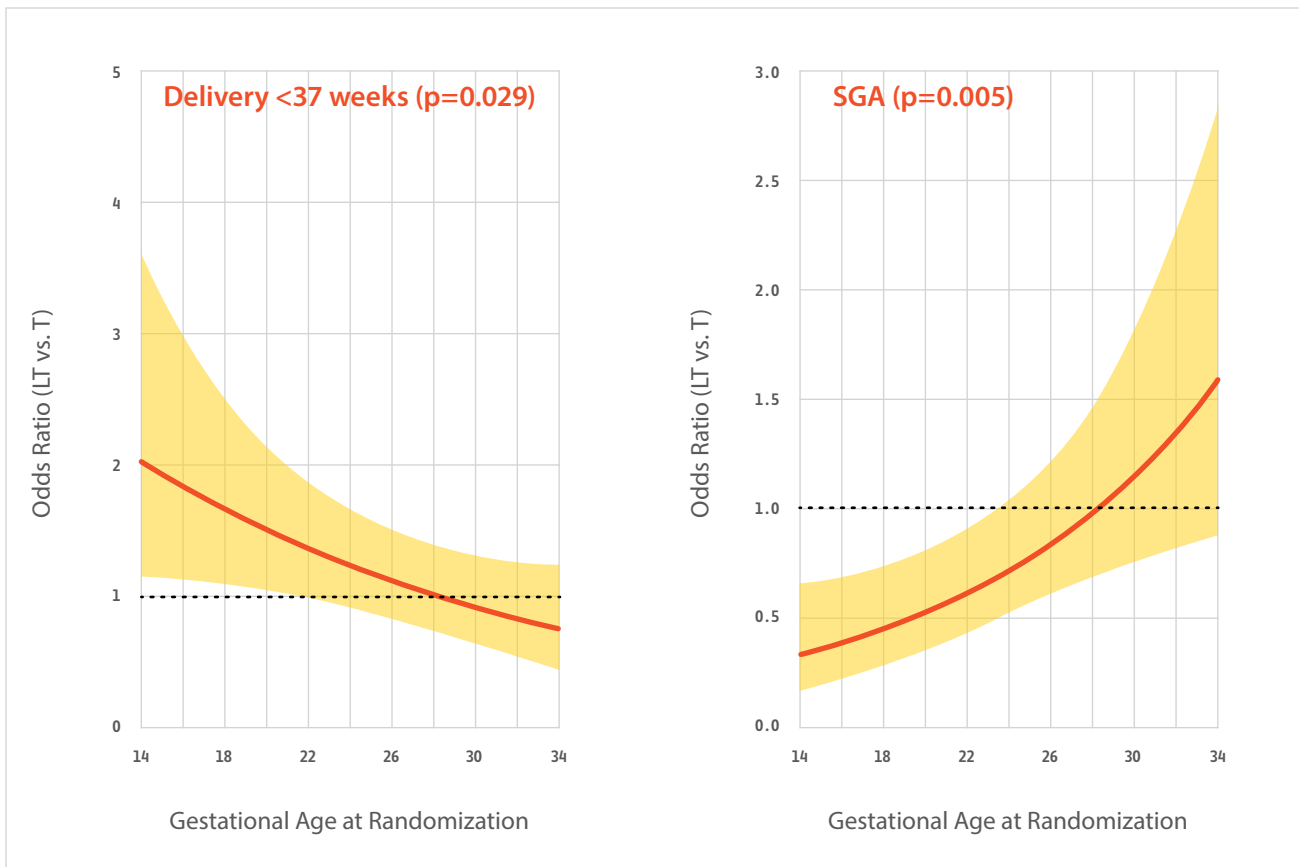
### Impact of Gestational Age at Randomization on Outcomes (Unpublished)

In collaboration with our lead Dutch investigators, we examined the impact of gestational age at randomisation (14+0 weeks to 33+6 weeks) on the major CHIPS outcomes, using mixed effects logistic regression. For the baby, randomisation before (but not after) 24 weeks' to 'less tight' (vs. 'tight') control was associated with more preterm birth ( $p=0.029$  for interaction between treatment and

time) (left), but fewer babies with birthweight <10th centile ( $p=0.005$  for interaction), and no effect on the primary perinatal outcome ( $p=0.636$  for interaction). For the mother, randomisation before 24 weeks' to 'less tight' (vs. 'tight') control was associated with more severe hypertension, with a diminishing effect thereafter ( $p=0.026$  for interaction). When to initiate antihypertensive therapy for non-severe pregnancy hypertension should not be guided by gestational age at less than 34 weeks.

### Is Pregnancy Hypertension Associated with Postpartum Haemorrhage? (Unpublished)

The most common serious maternal complication in CHIPS was blood transfusion (16/18 serious complications in 'less tight' and 8/10 in 'tight'). In the CLIP Pakistan Trial, verbal autopsies of maternal deaths have revealed that families of many women, who died from postpartum haemorrhage (PPH), reported that women had pre-eclampsia symptoms



ABOVE LEFT: The impact of gestational age at randomization on delivery <37 weeks.

ABOVE RIGHT: The impact of gestational age at randomization on SGA.

prior to the onset of bleeding. There is a published association between pre-eclampsia and PPH, but this has not been reflected in outcomes in pregnancy hypertension trials, and the causative pathways have not been explored. Using miniPIERS data, we have determined that the significant association between pre-eclampsia and PPH (OR of 2.01, 95% CI 1.02, 3.95) was mediated by low platelets and placental abruption, both of which were associated with PPH themselves. Adjustment for them (individually or together) negated the relationship between pre-eclampsia and PPH.

### Blood Pressure Level and Variability

BP level and variability have been associated with adverse cardiovascular outcomes, particularly for younger age groups and the outcome of stroke. In the CHIPS data, we found that higher BP was associated with worse perinatal and maternal outcomes, in both 'less tight' and 'tight' control groups. Also, measures of higher BP variability were consistently associated with worse maternal outcomes (serious maternal complications, severe hypertension, and pre-eclampsia) but better perinatal outcomes (primary perinatal outcome, birthweight <10th centile, and preterm birth) (presented International Society for the Study of Hypertension in Pregnancy 2016 and Royal College of Obstetricians and Gynaecologists World Congress 2017. Further collaboration is planned with the INTERBIO group in Oxford, United Kingdom.

### CHIPS Implementation

The next step is working towards implementation of a 'tight' BP control target in low and middle-income countries, using methyldopa as the antihypertensive.

Hutton E, Koren G, Lee SK, Logan AG, Ganzevoort JW, Welch R, Thornton JG, Moutquin JM. Control of Hypertension In Pregnancy Study randomised controlled trial—are the results dependent on the choice of labetalol or methyldopa?. *Br J Obstet Gynaecol.* 2016;123(7): 1135-41.

- Magee LA, Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Gafni A. Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the Control of Hypertension In Pregnancy Study (CHIPS) trial. *Br J Obstet Gynaecol.* 2015;123(7):1143–1151.
- Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Gafni A. Can adverse maternal and perinatal outcomes be predicted when blood pressure becomes elevated? Secondary analyses from the CHIPS (Control of Hypertension In Pregnancy Study) randomized controlled trial. *Obstet Gynecol Scand.* 2016;95(7):763–76.
- Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Pullenayegum E, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J. The cost implications of less tight versus tight control of hypertension in pregnancy (CHIPS Trial). *Hypertension.* 2016;68(4):1049–55.
- Vidler M, Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A. Women's views and postpartum followup in the CHIPS Trial (Control of Hypertension in Pregnancy Study). *Eur J Obstet Gynecol Reprod Biol.* 2016;206:105–113.

## Publications

- Magee LA, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Gafni A. The Control of Hypertension In Pregnancy Study (CHIPS) randomized controlled trial—is severe hypertension just an elevated blood pressure?. *Hypertension.* 2016.
- Magee LA; CHIPS Study Group, von Dadelszen P, Singer J, Lee T, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Gafni A, Gruslin A, Helewa M,



ABOVE: The CoLab team at the 2016 annual meeting.

Objective



Collaboration

# Objective 4: Collaboration Timeline

## 2011

- APR 01 2011 — Initial Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium



## 2012

- SEP 01 2012 — 2<sup>nd</sup> Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium

## 2013

- JUN 01 2013 — CoLab abstract published at ISSHP Meeting. Maternal circulating PIGF concentrations and placenta-related pregnancy complications: first results from the CoLab AngF Study

**Maternal circulating PIGF concentrations and placenta-related pregnancy complications: First results from the CoLab AngF Study** A.C. Staff, Ó. Burke, S. Benton, P. von Dadelszen, P. Szafranski, C. Zhang, C. Buhimschi, I. Cetin, F. Figueras, C. Holzman, C. Hubel, H. Laivuori, T. McElrath, Myers, R. Ness, L. Poston, C. Ris-Stalpers, J. Roberts, E. Schistermann, E. Steegers, S. Timmermans, J.A. van der Post, P.M. Villa, D. Williams, C. Redman (For the Global Pregnancy CoLaboratory of the PRE-EMPT Project)

**Introduction:** Circulating angiogenic factors are potential markers for preeclampsia, but heterogeneous studies have failed to identify precise predictive/diagnostic properties. The Global CoLaboratory is investigating how to merge published data of angiogenic factors for meta-analysis on an individual sample basis.

**Objective:** To amalgamate pregnancy angiogenic factor studies, investigate diagnostic and predictive properties of these markers in preeclampsia and placenta-related pregnancy complications, and to test if measures from disparate platforms can be standardised. This is the first report using PIGF measures to diagnose preeclampsia.

**Methods:** Data were derived from 15 cohorts, within and outside the CoLaboratory network.

- SEP 01 2013 — 3<sup>rd</sup> Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium

## 2014

- JAN 01 2014 — Position paper published: Burton GJ et al. Optimising Sample Collection for Placental Research. *Placenta* January 2014, Volume 35, Issue 1, Pages 9–22.
- MAY 01 2014 — LINK Registry: CoLab centers completed entering their data
- JUN 01 2014 — Position paper published: Myatt L, Redman CW, Staff AC, Hansson S, Wilson ML, Laivuori H, Poston L, Roberts JM (2014 Jun). Strategy for standardization of preeclampsia research study design. *Hypertension*, 63(6), 1293-1301.
- SEP 01 2014 — 4<sup>th</sup> Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium

## 2015

- JAN 01 2015 ○ Project led by Annetine conceived at the 2014 CoLab annual meeting was published: Extending the scope of individual patient data metaanalyses: Merging algorithms for biomarker measurements from heterogeneous laboratory platforms.
- JAN 01 2015 ○ Begin development of COLLECT database with MedSciNet

**Solution: COLLECT - The Global Collaboration Database**

Many obstetric problems, including preeclampsia, are complex syndromes with more than one subtype suggesting differing underlying pathogenic pathways. To unravel these complexities, large, statistically powerful datasets formed by merging many smaller studies are needed. Databases are expensive to design and maintain and often difficult/impossible to merge as different databases may be incompatible

**What we have done:**

The Global Pregnancy Collaboration (CoLab) has created a standard pregnancy database available for online use by interested investigators in both low and middle-income and in high-income countries.

- AUG 31 2015 ○ 5<sup>th</sup> Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium

## 2016

- APR 01 2016 ○ Papers published: Pregnancy and Long-term Cardiovascular Health: Progress through Harmonization of Research Cohorts and Biobanks
- APR 01 2016 ○ Position paper published: Collaboration to understand complex diseases: Preeclampsia and adverse pregnancy outcomes
- APR 01 2016 ○ Grand Challenge Thriving Children PrePARE Grant Funded
- APR 01 2016 ○ Funding Received: All Children Thriving (ACT) conduct proof of concept of Life Assay-PrCr Strip test. Biobank for long term storage in Stellenbosch University funded as part of this project
- JUN 01 2016 ○ EMPOWER Award supported by CoLab, Preeclampsia Foundation, and ISSHP funds Sarah Manyame with Jim Roberts as mentor
- AUG 26 2016 ○ 6<sup>th</sup> Annual Membership Meeting of thought leaders to plan future projects and activities and directions for the consortium
- SEP 01 2016 ○ Study completed and manuscript published: Fetal sex-specific differences in gestational age at delivery in pre-eclampsia: a meta-analysis

## 2017

- SEP 01 2017 ○ COLLECT database used in 3 research studies
- MAR 01 2017 ○ CoLab funds first seed grant: Sisters and Daughters of Women with Preeclampsia: A Cohort Study
- APR 01 2017 ○ Publication of proceedings of the 2015 CoLab Annual Meeting



- JUL 01 2017 ○ Proceedings 2016 CoLab Annual Meeting: Submitted to *Placenta*

# The Global Pregnancy Collaboration (CoLab)

**Principal Investigator:** Jim Roberts

**Funding:** Bill & Melinda Gates Foundation

## Overview

As I begin our discussion of the progress made in the Global Pregnancy Collaboration (CoLab) this period, I am reminded of the goals of this collaboration. The overall mission of CoLab is to improve the health of women and their infants by fostering collaborative research and the sharing of biological materials and data. Our efforts this year have been largely directed at low resource settings (LMIC) as described below. A major step forward toward this mission is serving as collaborators to Dr. Marcos Bastos Dias (PI) and his Brazilian colleagues in the PrePARE project, (Prematurity reduction by Pre-eclampsia cARE), funded by the CNPq/Gates Foundation Grand Challenges Brazil fund, that will translate biomarker-related and outcome prediction knowledge into clinical care through a stepped-wedge cluster randomised controlled trial design in health centres providing maternity care to women throughout Brazil. Dr. Dias and his team will also establish a biorepository of more than 7,000 samples to address future research in this population. The PrePARE cohort began in April 2017 and the trial was officially registered in March 2017, with the first centre to be randomised in July 2017.

Another area of strong progress this period is the COLLECT database, which has gone live and currently in use by three research studies. COLLECT is now available to investigators worldwide and is being publicized through editorials in major journals. A new initiative under development is the COLLECT Medical Birth Registry, which will be of particular benefit to LMIC. I am grateful to our CoLab members. It is through their tireless energy and creative efforts that we continue to move forward in our overall mission.

## Year 7 Progress

### New Members

**Dr. Joyce Browne:** CoLab welcomed Dr. Joyce Browne and her research group at the Julius Center for Health Sciences and Primary Care, Utrecht University, the Netherlands, to membership. Their interests are hypertensive disorders of pregnancy, prediction and prevention, prediction of other adverse pregnancy outcomes in the context of LMIC. They bring to the CoLab consortium a cohort of more than 1,000 women from Accra, Ghana. Dr. Browne also has collaborations in other African studies, with which we are currently establishing interactions.



**Dr. Carlos Escudero:** We are evaluating a new strategy by which we welcome consortia of several programs in low resource settings as one-member centre. Dr. Carlos Escudero of Universidad del Bío-Bío, Chillán, Chile, is leading a collaborative network of researchers interested in the study of pre-eclampsia and other adverse pregnancy outcomes. The group currently consists of 55 researchers from 8 Latin American countries and Spain including Argentina, Bolivia, Brazil, Chile, Colombia, Cuba, Ecuador, and Mexico. Dr. Escudero will serve as the representative member of the CoLab Steering Committee and serve as liaison with his group. We will work with him and his colleagues to get this collaborative consortium established

and productive, assisting with obtaining funding, providing procedures of operation and consultation on projects. Dr. Roberts visits the group in July 2017.



### COLLECT Database

The extensive work of Chris Redman and his CoLab database team have been successful and the COLLECT database has now been implemented in three studies and preparations for the usage are in place for several others. It is going live around the world. Editorials are in process for submission to Obstetrics and Gynecology, Pregnancy Hypertension, Hypertension, Placenta, *BJOG* and *COLLECT* will be highlighted on the CoLab website on the Global Health Network, <https://pregnancycolab.tghn.org>.

### Projects currently using COLLECT

1 **The Brazil PrePARE (Prematurity Reduction by Pre-eclampsia cARE) study** (PI: Dr. Marcos Bastos Dias) supported by the Brazilian Health Ministry and the Bill & Melinda Gates Foundation will be conducted in 7 large hospitals in different areas of Brazil. PrePARE has two arms: a cohort and an intervention study based on novel screening tests applied to women admitted for suspected pre-eclampsia. The cohort (recruits) will generate an important biobank, testing the sample management system of COLLECT. The intervention study (recruits) has a stepped-wedge design. This will utilise a modified RCT version of COLLECT. The database has been translated into Portuguese, amended to include the screening procedures and at this time, there are more than 80 recruits to the intervention arm

of the study, to measure the baseline for the stepped-wedge trial that is proposed.

- 2 **CHronic hypERTension and L-citRulline studY (CHERRY)** (PI: Jenny Myers; A randomised double-blinded feasibility study on the effects of L-citrulline on uteroplacental and cardiovascular function in hypertensive pregnant women sponsored by the Central Manchester University Hospitals NHS Foundation Trust and funded by the UK National Institute of Health Research. The database has been amended with five additional modules to address issues specific to the study needs. If the feasibility study is successful a full-scale trial is expected to follow.
- 3 **The role of air pollution in relation to pro-inflammatory and pro-oxidative tissue damaging mechanisms in pre-eclampsia (PE): a serious health care problem in low- and middle-income countries** (PI: Dr. Stefan Hansson). This air pollution study in Ethiopia is funded by the Swedish Research Council and sponsored by the Lund Medical School in Sweden to study the impact of indoor and outdoor air pollution during pregnancy. Recruitment of 2,000 participants is planned. This uses the minimal dataset with a new module specifically developed to record domestic and urban air quality measured in relation to a cohort of pregnant Ethiopian women.



- 4 Two CoLab members, Drs. Poston and von-Dadelszen, have received a large MRC grant: **PRECISE (PREgnancy Care Integrating translational Science,**

*Everywhere*) to establish consortia in Gambia and other African countries and will use COLLECT as their database.

- 5 We are collaborating with the WHO and they will facilitate the use of COLLECT in several research centres where they are working within LMIC.

### **The COLLECT Medical Birth Registry (MBR)**

Chris Redman is working to extend the concept of COLLECT to a COLLECT Medical Birth Registry (MBR). This follows several conversations with LMIC researchers who expressed concerns that even the minimal data set version of COLLECT is more than they can use at present. Chris and Annetine Staff visited Grootte Schuur (University of Cape Town [UCT]) and Tygerberg (University of Stellenbosch [US]) hospitals in February. The visit was funded by Oslo University in order to foster academic and research links between Norway and the Universities of Stellenbosch and Cape Town. The purpose of the visit was to explore the development of a CoLab MBR and testing it in Cape Town. Annetine and Chris also travelled under the umbrella of CoLab, as they presented the concept of the COLLECT Medical Birth Registry (MBR) and sought views on its applicability to South African maternity care. This would develop COLLECT in line with needs of LMIC. During the visit, the design of a new COLLECT electronic MBR was discussed in relation to the requirements of a proposed South African national register. The aim was agreed that a prototype could be built and tested in one or two hospital settings for UCT/US. If these tests were successful, testing would be extended for 3-6 months using an added pre-eclampsia screen. Similar collaborations and testing of CoLab Global MBR will be proposed according to CoLab planning and development, such as in South America, Indonesia and India. Following their February visit, they have continued their efforts to promote the development of the MBR and have travelled and met with many colleagues. We are also reaching out to the WHO for their assistance in facilitating this registry into low resource settings.

### **Potential Consortium and COLLECT in Indonesia**

CoLab members Drs. Jim Roberts, Chris Redman and Anne Catherine Staff will visit Indonesia (by invitation) in

October 2017 to address the formation of an Indonesian consortium similar to the group we are supporting in Latin America. We will also encourage the use of the COLLECT Medical Birth Registry in this setting. We have also begun exploring the possibility of a similar arrangement with investigators in Africa and India.

### **Air Pollution and Inflammation in Ethiopia**

In November 2015, CoLab member Dr. Stefan Hansson of Lund University began recruitment of a cohort in Ethiopia that will eventually comprise 2,000 pregnant women for his project, “The role of air pollution in relation to pro-inflammatory and pro-oxidative tissue damaging mechanisms in pre-eclampsia (PE): a serious health care problem in low- and middle-income countries. Women are recruited at Adama Regional Hospital and two urban health centres at the time of their first antenatal care visit. Following written consent plasma and later also placenta samples are collected and a standardised questionnaire is completed. Currently, they have collected 350 placental samples. All routine and study data are collected and entered into the CoLab COLLECT Database that has been specially adapted to include questions about air pollution specific to the project. The study team plans to measure exposure and collect air pollution particles in Adama. Air pollution in LMIC is an enormous and increasing health problem and these countries have the highest maternal mortality rates in the world. The overarching purpose of this translational project is to investigate exogenous factors in air pollution and to study how they induce



ABOVE RIGHT (L to R): PHD student Tsehayneh Kelemu and Dr Stefan Hansson.

oxidative stress and inflammation during pregnancy. Increased insight into pregnancy outcomes in relation to air pollution exposure is crucial to combat an increasing air pollution problem on maternal child health and morbidity.

### **Meeting of PrePARE (Prematurity Reduction by Pre-eclampsia cARE) Brazil Project**

On October 22, 2016, collaborating members of the CoLab Brazil PrePARE project met with the Brazilian PI, Dr. Marcos Bastos Dias as well as the other Brazilian site PIs. In addition to presentations by Drs. Jim Roberts, Peter von Dadelszen, Laura Magee, Lucy Chappell, Lucilla Poston, Arun Jeyabalan and Leandro Oliveira, there was an interactive and productive discussion in anticipation of the project kick-off in mid-2017. Jim Roberts and Arun Jeyabalan also enjoyed a three-day visit in Botucatu with co-investigator Leandro Oliveira. They had the opportunity to visit one of the PrePARE hospital sites as well as an associated community health clinic. They visited the proposed site of the biorepository in Botucatu and were impressed with the facility and in particular the safety features. They also met with very enthusiastic project team members in Botucatu, São Paulo.



Dr. Leandro Gustavo de Oliveira (centre) gave a presentation on the PrePARE study during Preeclampsia Day, 22/05/2017, pictured with residents at Botucatu São Paulo State University Medical School.



### **EMPOWER**

Dr. Sarah Manyame, our LMIC representative working in Zimbabwe, has been awarded an EMPOWER grant for her project, “Urine biomarkers for pre-eclampsia in high-risk women”. Cosponsored by the ISSHP, CoLab and the Board of Directors of the Preeclampsia Foundation, this EMPOWER award will provide funding and mentoring for beginning investigators in LMIC. Her project is to investigate concentrations of PIGF/sFlt-1, protein/creatinine ratios, calcium/creatinine ratios, and SERPINA-1 measured by Congo Red in the urine of hypertensive women in pregnancy. This work will be performed as a nested cohort study within the CAP Trial, and could provide a simple and inexpensive way to identify preeclamptic women in LMICs. Her mentor, Jim Roberts, recently visited Sarah during which time they created a timeline and began plans for performing these studies in Harare. They also visited Carmen Swanepoel who administers the CoLab African Biobank at the Tygerberg medical branch of Stellenbosch University. They examined the facility and began the exploration of the extension of Sarah’s study with a validation cohort with collaborators in Cape Town.

### **CoLab Seed Funding Award**

The CoLab Executive Committee recently approved the application submitted by Hilary Gammill, Eleni Tsigas, Roberta Ness and colleagues entitled: Sisters and Daughters of Women with Preeclampsia: a Cohort Study. The Preeclampsia Foundation has been working with

ABOVE LEFT: The PrePARE Brazil meeting at ISSHP, October 2016

ABOVE RIGHT: Leandro Oliveira presents the PrePARE trial on World Preeclampsia Day.



CoLab to develop a proposal for a pilot study to ascertain the feasibility of conducting a large-scale cohort study of sisters and daughters of women with pre-eclampsia. The overarching goal of this line of investigation is to determine whether pre-eclampsia directly causes cardiovascular disease or whether both arise from shared risk factors. Studies of women at risk for pre-eclampsia before their first pregnancy provide a unique opportunity to definitively answer this question. This cohort will also provide a unique opportunity to test prepregnancy interventions on a moderately high-risk group. The feasibility study will test The Preeclampsia Registry's (TPR) ability to enroll and maintain engagement of nulliparous sisters or daughters of women with a history of pre-eclampsia (and controls). Such a study requires large numbers of women and will be done with the participation of BabyCenter a pregnancy website contacted by 70% of pregnant women in the United States. TPR is uniquely poised to inform research and clinical efforts with an

enthusiastic community and committed support from its communication partner, BabyCenter, which reaches more than 45 million parents per month. This innovative strategy of using social media to facilitate massive recruitment if successful would provide a remarkable resource for future studies.

### **AWARE (Angiogenic factors Will Assist in Risk Evaluation)**

CoLab is working with Dr. Leandro Oliveira who has received funding from Roche Diagnostics for a study using samples from the PrePARE biorepository. The study addresses the potential usefulness of PlGF to stratify risk in apparently low-risk women at 28 to 32 weeks of gestation. The study will also provide supplementation for the PrePARE study and administrative support to CoLab.



### **PRECISE (Pregnancy Care Integrating Translational Science, Everywhere) Network: A Sub-Saharan Network for Placental Disorders**

Many CoLab members, especially Peter von Dadelszen, Laura Magee and Lucilla Poston, have received a large Research Councils of the UK grant. Several CoLab resources including the COLLECT database, consortium biological samples and the standardised protocol for

placental sampling and tissue storage (Optimising sample collection for placental research, GJ Burton, et al; *Placenta* 35 (2014) 9-22) will be utilised in this study. In a letter from Jim Roberts in support of the project and on behalf of the CoLab, he invites the PRECISE consortium to CoLab membership.

### **All Children Thriving: South Africa (ACT)**

The biorepository in South Africa has become a reality. CoLab partnered with the PRE-EMPT CAP study to work with Life Assay Diagnostics to field test an inexpensive protein/creatinine test strip for use in the field. As part of this project, study samples and future samples from Africa will be stored at a world-class biobank (Stellenbosch University H3 biobank). This centre will also be used to store samples from the CAP study.

## Collaboration and Potential Funding

### **Bolivian Pre-eclampsia Grant:**

**Principal Investigator:** Professor Lorna Moore

We are working on several potential collaborative projects. A colleague whose group has been working in Bolivia for many years (since 1999) contacted us regarding a NIH proposal they are submitting. This proposal was for a project in Bolivia to update their diagnosis and treatment of pre-eclampsia, and its implications for later life cardiovascular disease and to create a pilot perinatal registry and conduct a pilot study. CoLab agreed to support the application and if funded, assist in creating workshop(s) to address both updating diagnostic criteria for pre-eclampsia and other hypertensive disorders of pregnancy and their sequelae for maternal and infant health. These workshops will address the importance of extending such knowledge to LMIC, and especially countries like Bolivia where hypertensive disorders of pregnancy are one of the major contributors to Bolivia's infant and maternal mortality, which is the highest in South America. We will also provide the COLLECT database (translated into Spanish) and the planned Medical Birth Registry module, a subset of the minimal database, to enable acquisition of obstetrical information at time of delivery in standardised way with the advantages

of ease of integration with other institutions worldwide and if in the future they would need to upgrade to the minimal dataset for future studies, it could be done easily.

### **Syncytiotrophoblast Microvesicles and Danger Associated Molecular Patterns in Pre-eclampsia Related Preterm Delivery**

Dr. Brandie DePaoli Taylor, Principal Investigator on a current CoLab project, recently submitted an application to the Burroughs Wellcome Fund. If the project is funded, CoLab member Jenny Myers of the SCOPE cohort has agreed to provide 840 samples. A budget for acquiring these samples was included in the BWF application.

### **Urinary Adipsin as a Pre-eclampsia Diagnostic**

CoLab is working with PATH to submit a grant to test urinary adipsin as a point of care assay for pre-eclampsia detection that is more easily interpreted than standard colour strips. Preliminary experiments by CoLab with PATH are encouraging.

### **Sustainability Efforts**

In addition to funding on collaborative grants we continue to explore projects with industry. We recently provided a letter of support to collaborate with Metabolomic Diagnostics Ltd on PRESEDE: PREgnancy Screening offers Early DETection of Preeclampsia Risk, a study of diagnostic screening tests for pre-eclampsia that they are developing. We would work with them to ascertain that possible cohorts are compliant with the required sample quality requirements as well as having the relevant clinical metadata collected. We are assisting in the upcoming project as a proof of principle. As we strive to make CoLab self-sustaining, we plan on embarking on activities such as this as a means toward achieving this goal.

CoLab has also received support from the AWARE, PrePARE and ACT grants.

Administrative support for CoLab has been included on 6 projects for which we have provided samples.

### **Highlights of Ongoing CoLab Projects**

We are proud to continue support of several projects from investigators in and outside of CoLab. A list of on-going projects is included in the Appendix C.

## **Prediction and Prevention of Pre-eclampsia and Intrauterine Growth Restriction (PREDO) Study**

**Principal Investigator:** Lucy Chappell

**Co-Investigators:** Kate Bramham, Lucilla Poston, Hannele Laivuori

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Chronic hypertension is an increasing medical complication and it predisposes pregnant women to superimposed pre-eclampsia, which is associated with adverse outcomes for both the mother and fetus. Maternal adverse outcomes include acute renal failure, cardiovascular or respiratory dysfunction, coagulation dysfunction, stroke, eclamptic seizure, or even maternal death. Fetal adverse outcomes include stillbirth, low birth weight, low Apgar score and neonatal complications due to premature delivery. However, only few studies before have explored the underlying mechanisms of superimposed pre-eclampsia in women with chronic hypertension. We have now studied these mechanisms in a relatively small, but well-characterised prospective Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) Study cohort with longitudinal sampling. The estimation of endothelial surface layer, the glycocalyx function in women with chronic hypertension has not been previously attempted. We found that a glycocalyx constituent, syndecan-1, is decreased together with plasma placental growth factor concentration and urine albumin:creatinine ratio is increased in women who subsequently developed superimposed pre-eclampsia. These findings implicate endothelial glycocalyx disturbance and reduced angiogenic capacity as predisposing factors for superimposed pre-eclampsia. Restoration of glycocalyx could even provide an opportunity for therapeutic intervention. The manuscript “Predisposition to superimposed pre-eclampsia in women with chronic hypertension: a role for endothelial and placental factors” by Kate Bramham, Pia M Villa, Hannele Laivuori, Esa Hämäläinen, Eero Kajantie, Katri Räikkönen, Anukatriina Pesonen, Paul Seed, R Neil Dalton, Charles Turner, Max Wong, Peter von Dadlezen, James Roberts, Lucilla Poston, Lucy Chappell has been submitted to the British Medical Journal Open in May 2017.

## **Sisters and Daughters of Women with Pre-eclampsia: A Cohort Study**

**Principal Investigators:** Hilary S. Gammill, Roberta Ness, James M. Roberts, Eleni Tsigas

**Co-investigators:** Alina Brewer, Kasey Dickenson, Ingrid Granne, Chris Redman

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CoLab is supporting and working with The Preeclampsia Registry (TPR) to ascertain the feasibility of conducting a large-scale cohort study of sisters and daughters of women with pre-eclampsia. The overarching goal of this line of investigation is to determine whether pre-eclampsia directly causes cardiovascular disease or whether both arise from shared risk factors. Studies of women at risk for pre-eclampsia before their first pregnancy provide a unique opportunity to definitively answer this question. The feasibility study will evaluate the ability of TPR in conjunction with its communication partners, to enrol and maintain engagement of nulliparous sisters or daughters of women with a history of pre-eclampsia (and controls).

Since receiving funding in March 2017, TPR has been focussed on performing an upgrade of TPR’s mobile capabilities and user interface. This will be key for successful enrollment, engagement, and follow-up. Marketing and recruitment strategies are being developed with PF’s communication partner, BabyCenter, which reaches more than 45 million parents per month online. The protocol modification, consent forms, and questionnaires are being drafted for IRB review in July 2017. It is anticipated that recruitment for this study will begin in August 2017.

## **Linking Fertility (IVF) and Pregnancy Repository Linkage**

**Co-Principal Investigators:** Thomas McElrath, Mark Santillan

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This is a collaborative project of two CoLab members Mark Santillan (University of Iowa) and Thomas McElrath (Harvard University). Currently, they have linked their IVF and pregnancy registries and have the ability to follow 400+ pregnancies from pre-pregnancy through delivery. They are investigating the effects of trophectodermal manipulation on placentation and pregnancy outcome. They plan on reconvening at 2017 CoLab Annual Meeting.

## Microparticle Proteomics as a Marker for Impending Preterm Birth

Principal Investigator: Thomas McElrath

This project seeks to validate existing work indicating the ability to predict spontaneous preterm birth using the protein signature of microparticles gathered at 12 weeks gestation. We have been able to recruit multiple samples through CoLab partners including GAPPs and Magee Womens Hospital. The confirmatory results are highly encouraging and were presented as a poster at the 2017 SRI Conference. We will present additional results at the 2017 annual CoLab meeting. Samples are presently under analysis with manuscripts in preparation. We anticipate examining the exosomal proteome for pre-eclampsia related markers as well.

### Year 8 Deliverables

In the coming year, we will seek additional funding to expand our activities. This includes a revision of COLLECT to form and distribute a concise COLLECT registry to LMIC settings in collaboration with the WHO. We will work with Indonesian investigators to establish a consortium in this setting that would unitize COLLECT and the registry. If sufficient funding is available, we will work with consortia in Latin America and Indonesia to establish a training program for future research leaders in these countries.

We will strengthen collaborative interactions with other groups working with LMIC and specifically expand interactions with neonatal investigators in LMIC to facilitate a smooth transfer of information about the neonate from pregnancy into early life.

We continue on-going projects with special efforts to “market” COLLECT to investigators in low and high resource settings worldwide. We will explore expanded avenues to generate other funds for CoLab through collaborative research and commercial interactions.

### 2017 CoLab Meeting

Planning and preparations continue for the CoLab annual membership meeting to be held October 2-3, 2017 as part

of the large PRE-EMPT Sixth Annual Meeting at the Sheraton Heathrow Hotel in London, United Kingdom. The theme for the Scientific Workshop is Prepregnancy and pregnancy nutrition. Speakers have been invited. Examples of topics include calcium in pregnancy, obesity in high and low resource settings, sodium in pregnancy revisited and insulin resistance and a panel discussion of special challenges of nutritional research in low resource settings.

### Publications

- Roberts JM, Hansson SR, Vaiman D, Redman CW, Global Pregnancy Collaboration. Global Pregnancy Collaboration symposium on placental health: Summary and recommendations. *Placenta*. 2017.
- Vaiman D. Genes, epigenetics and miRNA regulation in the placenta. *Placenta*. 2017;52:127-33.
- Tannetta D, Collett G, Vatish M, Redman C, Sargent I. Syncytiotrophoblast extracellular vesicles—Circulating biopsies reflecting placental health. *Placenta*. 2017 Apr 30;52:134-8.
- Sebire NJ. Implications of placental pathology for disease mechanisms; methods, issues and future approaches. *Placenta*. 2017;52:122-6.
- Cox LS, Redman C. The role of cellular senescence in ageing of the placenta. *Placenta*. 2017;52:139-45.
- Burton GJ, Yung HW, Murray AJ. Mitochondrial—Endoplasmic reticulum interactions in the trophoblast: Stress and senescence. *Placenta*. 2017;52:146-55.

### Published Abstracts

- Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, Ward K. Cardiomyopathy and preeclampsia: Shared genetics? *Reproductive Sciences*, 2017. 24: 286A (poster presentation) 64th Annual Scientific Meeting of the Society for Reproductive Investigation.
- Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, Ward K. Identification of novel genetic variants from whole exome sequencing in preeclampsia.

*Reproductive Sciences*, 2017. 24: 221A (poster presentation) 64th Annual Scientific Meeting of the Society for Reproductive Investigation.

- Gammill HS, Chettier R, Brewer A, Roberts JM, Shree R, Tsigas E, Ward K. Three protein-truncating mutations that may contribute to developing preeclampsia. *Reproductive Sciences*, 2017. 24: 68A (oral presentation) 64th Annual Scientific Meeting of the Society for Reproductive Investigation.

## 2016-2017 CoLab Member Presentations

- Jim Roberts delivered the keynote address at the American Physiological Society Workshop: Novel genetic risk factors and early pregnancy mechanisms contributing to preeclampsia on the topic Pregnancy: What next? In this, he addressed the need for collaboration for solving complex problems such as pre-eclampsia and highlighted the role of CoLab and COLLECT and pointed out their availability to investigators worldwide.
- Jim Roberts: University of Iowa, Center for Hypertension Research, Pregnancy an indicator of cardiovascular risk: Potential mechanisms for later life cardiovascular disease and Reducing preterm births in Brazil through objective assessment: The PrePARE Study, November 17-18, 2016.

- Jim Roberts: ISSHP World Congress, Sao Paulo, Brazil, PrePARE: Prematurity reduction by pre-eclampsia care, October 2016.
- Chris Redman: COLLECT Database; Euro Tox Talx, Oxford, UK, September 2016.
- Chris Redman: COLLECT Database, ISSHP World Congress, Sao Paulo, Brazil, October 2016
- Chris Redman and Annetine Staff: Three presentations on COLLECT during a CoLab/University of Oslo/Oxford sponsored visit to Cape Town, South Africa, February 2017.

## Public Relations

We continue to update and grow our website on the Global Health Network <https://pregnancycolab.tghn.org/> with information about CoLab projects, publications, and member centres, and other areas of interest. The site will be extremely useful for getting our message out about collaboration and the CoLab COLLECT database and proposed COLLECT Medical Birth Registry, especially in LMIC. An informative editorial about COLLECT will be posted in the coming days.

Several CoLab members took the opportunity at local, national and international meetings to promote CoLab and the COLLECT database.



ABOVE: Discussion at the CoLab Meeting 2016 in Oxford.

# The PRECISE (PREgnancy Care Integrating Translational Science, Everywhere) Network: a Sub-Saharan Network for Placental Disorders

**Principal Investigator:** Peter von Dadelszen

**Funding:** The Research Councils of the UK Grand Challenges Research Fund

**Partner Institutions:** Kings College London, Medical Research Council Gambia, Aga Khan University Nairobi, Centro de Investigação em Saúde de Manhiça, The World Health Organization, University of British Columbia, Donna Russell Consulting, and Midland State University

A CoLab-related initiative, the PRECISE Network, is a new and broadly-based group of research scientists and health advocates mainly based in the UK and Africa, but also including the World Health Organization, UBC, and Donna Russell Consulting. We will establish this network through a shared project that will investigate three important complications of pregnancy, namely high blood pressure (hypertension), babies who are smaller than they should be before birth (fetal growth restriction) and babies who die before birth (stillbirth). We think that about 46,000 women and two-and-a-half million babies (both before and after birth) die due to these problems every year, and half of them die in Africa. In addition, about 50 million women and babies will have their short- and long-term health altered because of these complications. These numbers represent one of the great global inequalities of our time.

In developed countries like the UK, we know that these three pregnancy complications are caused by problems with the afterbirth (placenta), and we know quite a lot about how they develop and complicate pregnancies.

In contrast, we know very little about how and why these placental conditions occur in sub-Saharan Africa. This is especially complex as women in Africa often have many other challenges: limited diets that change with the seasons, chronic infections such as HIV or malaria, acute infections like Ebola, limited power to make decisions for themselves, life in communities that are prone to either flooding or drought and are remote from health facilities. Therefore, the way that pregnancy complications arise are probably very different for these women in sub-Saharan Africa, compared with women living in the more-developed countries. Yet, these women and their babies bear most of the burden of

death and illness related to pregnancy complications. We need to address this area of neglected global health research.

In PRECISE, we will train and mentor junior investigators in how to do pregnancy research, and we will establish new databases related to pregnant and some non-pregnant women, the context of their lives, their pregnancy complications and what happens at the end of their pregnancies. We will save samples of blood, urine and placental tissue, and test them to increase our knowledge about how women's bodies cope with both normal and complicated pregnancies. All the samples and the data will remain in Africa for use primarily by Africans in collaboration with UK-based and other scientists.

To have a sample of pregnancies that are typical of women in sub-Saharan Africa, we will invite about 12,000 women in The Gambia and Senegal (West Africa), Kenya (East Africa) and Mozambique (Southern Africa) to share their stories, the data related to their pregnancy and babies, and their blood, urine and placental samples with their regional team and the wider global research community, especially the PRECISE scientists. This large number of women will allow us to gain new and important insights into how and why women in sub-Saharan Africa develop these pregnancy complications, and how and why may of them and their babies die from these complications.

Through these activities, we hope to improve the health and well-being of women and their families in Africa, to build resilience to environmental events such as flooding or infectious disease outbreaks, to advise about where infrastructure such as roads will improve pregnancy outcomes, and to reduce the inequality of maternal and child deaths that is visited on families in sub-Saharan Africa.

# TraCer Project

**Principle Investigators:** Aris Papageorgiou, Alison Noble, Peter von Dadelszen, Mohammad Maraci

## Overview

The overall aim is to create a Transverse Cerebellar (TraCer) mHealth platform to calculate the best estimate of gestational age; using a prototype medical ultrasound-based tool. This is based on using a portable ultrasound probe and smartphone/tablet device to:

- Automatically measure the fetal transverse cerebellar diameter (TCD) using 2D ultrasound at 18-24 weeks using image analysis within a set protocol;
- Following the measurement using the TraCer image analysis, automated determination of gestational age (GA) based on this measurement (by using a lookup table relating TCD to GA).

## Progress

- 1 Automatic identification of the transverse cerebellar (TC) plane on 2D ultrasound

This first step of the analysis pipeline supports user guidance to the correct imaging plane. A simple clinical protocol was developed. Using images obtained from real life practice, (n=5,000) a machine-learning algorithm was designed and trained in order to automatically identify the fetal TC plane from candidate 2D obstetric ultrasound images.

- 2 Automatic identification of the TCD plane in an ultrasound video sweep

Once the TraCer image analysis tool was able to automatically recognize a 2D ultrasound image of the TC imaging plane of the fetal head, we moved to recognizing TC images within a real-time video “sweep” of the maternal abdomen.

- 3 Automatic identification of the TC diameter (TCD)

Once the 2D ultrasound image of the TC plane was able to be recognized using the TraCer image analysis tool, an

algorithm was trained to automatically detect and localize the TCD structure within the TC image.

- 4 Automatic / semi-automatic caliper placement for measurement of the TCD

Once a bounding box with the TC structure is located, a caliper needs to be placed for measurement. By comparing to a large number of “ground truth” data (n=2,700), it was possible to do this automatically, allowing manual correction (semi-automatic) when required.

- 5 Measurement chart relating TCD to GA;

In order to assess the correlation between the TCD and gestational age, in the form of a gestational age chart, we undertook a systematic review of the literature; this showed that there are 32 available charts. Analysis of the variation between charts as well as quality assessment was undertaken and demonstrated significant disagreement. In view of this, and in order to create a chart for use throughout gestational age, we used image data from the INTERGROWTH-21st study in order to create a high quality chart from prospectively recruited women.

- 6 Development of an app integrating all the above

We have designed and developed an app, which contained the above requirements.

- 7 Market research to identify most suitable probes for integration with APP

In order to integrate the app on a mHealth platform connected to a low cost ultrasound device, we have undertaken an in-depth scoping exercise of available low cost devices, and an evaluation of shortlisted systems to select one for trial.

## Next Steps

Having successfully automated ultrasound (US) measurement of the TCD for GA estimation, we have applied for Phase II funding to

- 1 Integrate the software into a low-cost mobile ultrasound system
- 2 Identify what level of healthcare worker can reliably use the system and
- 3 Pilot its implementation in a LMIC setting. At the end of Phase II we will be well placed to test the clinical value of the system through an appropriately powered and designed stepped-wedge cluster RCT.



ABOVE: A community health worker provides health education to a pregnant woman in her home in rural Mozambique.

Objective



Knowledge Translation

# The Preeclampsia Foundation

**Executive Director:** Eleni Tsigas



## Overview

Established in 2000, the Preeclampsia Foundation works to eliminate maternal and infant illness and death due to pre-eclampsia, HELLP syndrome, and other hypertensive disorders of pregnancy. We envision a world where pre-eclampsia no longer threatens the lives of mothers and their babies, and we accomplish important milestones every year. As a patient-centred organisation, we advocate on behalf of the thousands of families who have been—or will be—impacted by this life-threatening condition.

Together with an engaged community of survivors, volunteers, and donors, we represent the patient voice in an increasingly complex healthcare environment. Our dedicated Board of Directors and expert Medical Advisory Board guide our efforts to raise public awareness, provide patient education and support, improve healthcare practices, and catalyse and fund research. As we approach our third decade of existence, we remain as committed as ever, expanding our reach and resources thanks to growing partnerships and influence.

In our collaboration with the University of British Columbia and King's College London, we have enhanced our ability to reach out to women and families in low- and middle-income countries (LMICs). We also continue to advance pre-eclampsia-focussed research by LMIC-based clinicians and scientists, who represent such an important weapon in the global fight against pre-eclampsia.

Executive Director Eleni Tsigas has led the Preeclampsia Foundation to its current position as a sustainable, mission-driven, results-oriented organisation, and serves as a member of the PRE-EMPT Technical Advisory Group (TAG) and the Knowledge Translation (KT) working group.

## Year 7 Progress

### **Preeclampsia Foundation Canada Affiliate Introduced**

The Preeclampsia Foundation's commitment to raising public awareness extended into Canada with the introduction of Preeclampsia Foundation Canada. The new Canadian affiliate shares the Foundation's mission to eliminate maternal and infant illness and death due to pre-eclampsia, HELLP syndrome, and other hypertensive disorders of pregnancy.

Similar to the inception of the organisation in America more than 15 years ago, a group of committed pre-eclampsia and HELLP syndrome survivors worked together to form Preeclampsia Foundation Canada. These inspired individuals recognised the need for a national organisation to serve as a resource and collective voice for Canadian women and families affected by hypertensive disorders of pregnancy. Preeclampsia Foundation Canada is leveraging the brand awareness, visibility, history, and success of the Preeclampsia Foundation in its mission to improve patient education and fund new research.



### **Preeclampsia Awareness Month Focuses on Maternal Health Legislation**

The Preeclampsia Foundation's awareness efforts in the United States during Preeclampsia Awareness Month in May focussed on building grassroots support for bipartisan maternal health legislation. Introduced in both the House of Representatives and Senate, the legislation

aims to help states end maternal death, and to address the devastating and costly health consequences that threaten the lives of moms and their babies.

The U.S. ranks 47th globally for its maternal mortality rate, and women die every day in the U.S. due to complications from childbirth. Pre-eclampsia, HELLP syndrome, and related hypertensive disorders of pregnancy are a leading cause of maternal death, and for every death, there are at least 50 times more cases of adverse outcomes. Significant health disparities exist in the U.S.: black women are three to four times more likely to die from a pregnancy-related complication like pre-eclampsia than white women are.

*The House Preventing Maternal Deaths Act of 2017* and *Senate Maternal Health Accountability Act of 2017* seek to mitigate these statistics by supporting Maternal Mortality Review Committees. The legislation also promotes national information sharing through the Centers for Disease Control and Prevention (CDC) so that states can continue to learn from best practices and collaborate with each other.

Using the theme *#Act2SaveMoms*, the Preeclampsia Foundation's website features detailed information about this legislation at [www.preeclampsia.org/Act2SaveMoms](http://www.preeclampsia.org/Act2SaveMoms). Additional efforts to promote the legislation focussed on social and traditional media, guest blogs for several partner organisations including BabyCenter and Lamaze International Science & Sensibility, and a sign-on letter endorsed by more than three dozen maternal health organisations.



### First-ever World Preeclampsia Day Builds Global Awareness

To raise global awareness of pre-eclampsia, maternal health organisations around the world joined forces to host the first-ever World Preeclampsia Day on Monday, May 22. Co-sponsors BabyCenter, Ending Eclampsia/USAID, the International Society for the Study of Hypertension in Pregnancy (ISSHP), and PRE-EMPT joined the

Preeclampsia Foundation to reduce preventable deaths from pre-eclampsia.

As stated in a proclamation endorsed by World Preeclampsia Day co-sponsors and many other maternal health organisations, *"We join together to bring to light the relatively high prevalence and devastating impact of pre-eclampsia and other hypertensive disorders of pregnancy. These disorders are not rare complications of pregnancy; indeed, they affect 8-10% of pregnancies worldwide."*

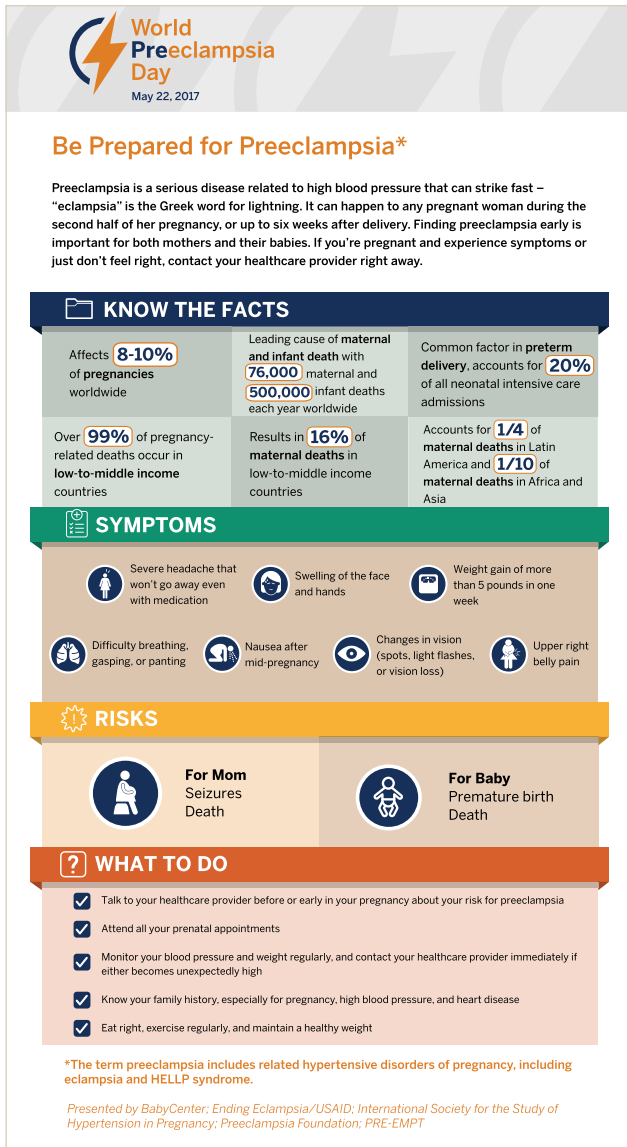
Using the theme 'Be Prepared Before Lightning Strikes', World Preeclampsia Day promotion activities focussed on a dedicated web page at [www.endingeclampsia.org/world-preeclampsia-day](http://www.endingeclampsia.org/world-preeclampsia-day) that featured a widely shared infographic and proclamation endorsed by 30 global maternal health organisations. As part of a far-reaching social media campaign, the Preeclampsia Foundation hosted a "Thunderclap" on the day of World Preeclampsia Day, May 22; this first-ever event was supported by 677 supporters and achieved a social reach of 577,729. The Foundation's *7 Symptoms Every Pregnant Woman Should Know* video was viewed at least 18,000 times during the campaign.

Participating organisations around the world extensively shared World Preeclampsia Day social media content and hosted events and activities in their local communities.



ABOVE LEFT: PE Foundation image.

ABOVE RIGHT: First-ever World Preeclampsia Day builds global awareness.



**World Preeclampsia Day**  
May 22, 2017

### Be Prepared for Preeclampsia\*

Preeclampsia is a serious disease related to high blood pressure that can strike fast – “eclampsia” is the Greek word for lightning. It can happen to any pregnant woman during the second half of her pregnancy, or up to six weeks after delivery. Finding preeclampsia early is important for both mothers and their babies. If you’re pregnant and experience symptoms or just don’t feel right, contact your healthcare provider right away.

#### KNOW THE FACTS

Affects <b>8-10%</b> of pregnancies worldwide	Leading cause of <b>maternal and infant death</b> with <b>76,000</b> maternal and <b>500,000</b> infant deaths each year worldwide	Common factor in <b>preterm delivery</b> , accounts for <b>20%</b> of all neonatal intensive care admissions
Over <b>99%</b> of pregnancy-related deaths occur in <b>low-to-middle income</b> countries	Results in <b>16%</b> of <b>maternal deaths</b> in low-to-middle income countries	Accounts for <b>1/4</b> of <b>maternal deaths</b> in Latin America and <b>1/10</b> of <b>maternal deaths</b> in Africa and Asia

#### SYMPTOMS

- Severe headache that won't go away even with medication
- Swelling of the face and hands
- Weight gain of more than 5 pounds in one week
- Difficulty breathing, gasping, or panting
- Nausea after mid-pregnancy
- Changes in vision (spots, light flashes, or vision loss)
- Upper right belly pain

#### RISKS

- For Mom:** Seizures, Death
- For Baby:** Premature birth, Death

#### WHAT TO DO

- ✓ Talk to your healthcare provider before or early in your pregnancy about your risk for preeclampsia
- ✓ Attend all your prenatal appointments
- ✓ Monitor your blood pressure and weight regularly, and contact your healthcare provider immediately if either becomes unexpectedly high
- ✓ Know your family history, especially for pregnancy, high blood pressure, and heart disease
- ✓ Eat right, exercise regularly, and maintain a healthy weight

\*The term preeclampsia includes related hypertensive disorders of pregnancy, including eclampsia and HELLP syndrome.  
Presented by BabyCenter; Ending Eclampsia/USAID; International Society for the Study of Hypertension in Pregnancy; Preeclampsia Foundation; PRE-EMPT



### Ghana

The Ghana Action on Preeclampsia Campaign Project, an initiative of the Center for Constitution Order, was launched concurrently with World Preeclampsia Day at the 37 Military Hospital Greater Accra Region. This event initiated the campaign of raising awareness of pre-eclampsia and its symptoms and impact on the lives of mothers, babies, and families globally and in Ghana and the sub-region.



Here is just a sample of worldwide activities held in recognition of World Preeclampsia Day.

### Australia

The St. George Obstetric Medicine Research team in Sydney hosted a public forum, during which two women who experienced pre-eclampsia shared their stories. Other topics included a general talk on hypertension in pregnancy and its management, the long-term risks of pre-eclampsia, and the team’s P4 study addressing those risks. Melbourne hosted a public event as well.

### Ireland

Three major stories relating to the INFANT Centre and pre-eclampsia were published on May 22. These stories focussed on pre-eclampsia and its symptoms as well as two case studies and descriptions of the research underway in the INFANT Centre to combat the condition. Combined with this, the INFANT Centre team launched a social media campaign, hosted a coffee morning for the staff of the maternity hospital, and arranged for six landmark buildings in Ireland to be lit up in orange (the colour theme of World Preeclampsia Day).

ABOVE LEFT: The World Preeclampsia Day Infographic was used to share key health information and increase awareness of pre-eclampsia.

ABOVE TOP RIGHT: The public forum on pre-eclampsia hosted by the St. George Obstetric Medicine research team in Sydney, Australia.

ABOVE BOTTOM RIGHT: The team of the Ghana Action on Preeclampsia Campaign.



## New Zealand

The New Zealand Action on Pre-eclampsia (NZAPEC) team thoroughly enjoyed raising awareness during May and participating in the Thunderclap campaign and World Preeclampsia Day. On May 22, they went out and about in Christchurch and Auckland visiting Midwifery Schools and midwifery practices, presenting at hospital education fora, and hosting an Open Café drop-in. They communicated with midwives and consumers through professional networks and several social media platforms, especially Facebook with weekly updates through the month of May. The team was also excited to launch a new book (*Understanding Pre-eclampsia—A Guide for Parents and Health Professionals*), co-authored by Joyce Cowan, NZAPEC's founder, Professor Chris Redman, and Isabel Walker.

## Uganda

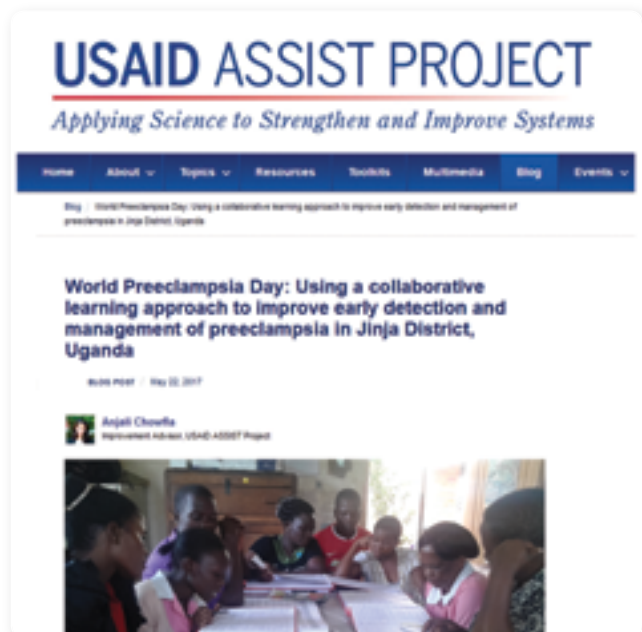
USAID ASSIST project, implemented by University Research Co. LLC, developed a blog on its ANC/PEE improvement work in Uganda. They also featured a page on the ASSIST website dedicated to World Preeclampsia Day, where they shared four things you can do to learn more about pre-eclampsia at [www.usaidassist.org/content/world-preeclampsia-day](http://www.usaidassist.org/content/world-preeclampsia-day), and posted information about pre-eclampsia on ASSIST social media channels using the global hashtag #worldpreeclamsiaday.

## Research Initiatives Continue to Move Forward

The Preeclampsia Foundation's focus on advancing research remains a strong commitment as we strive to

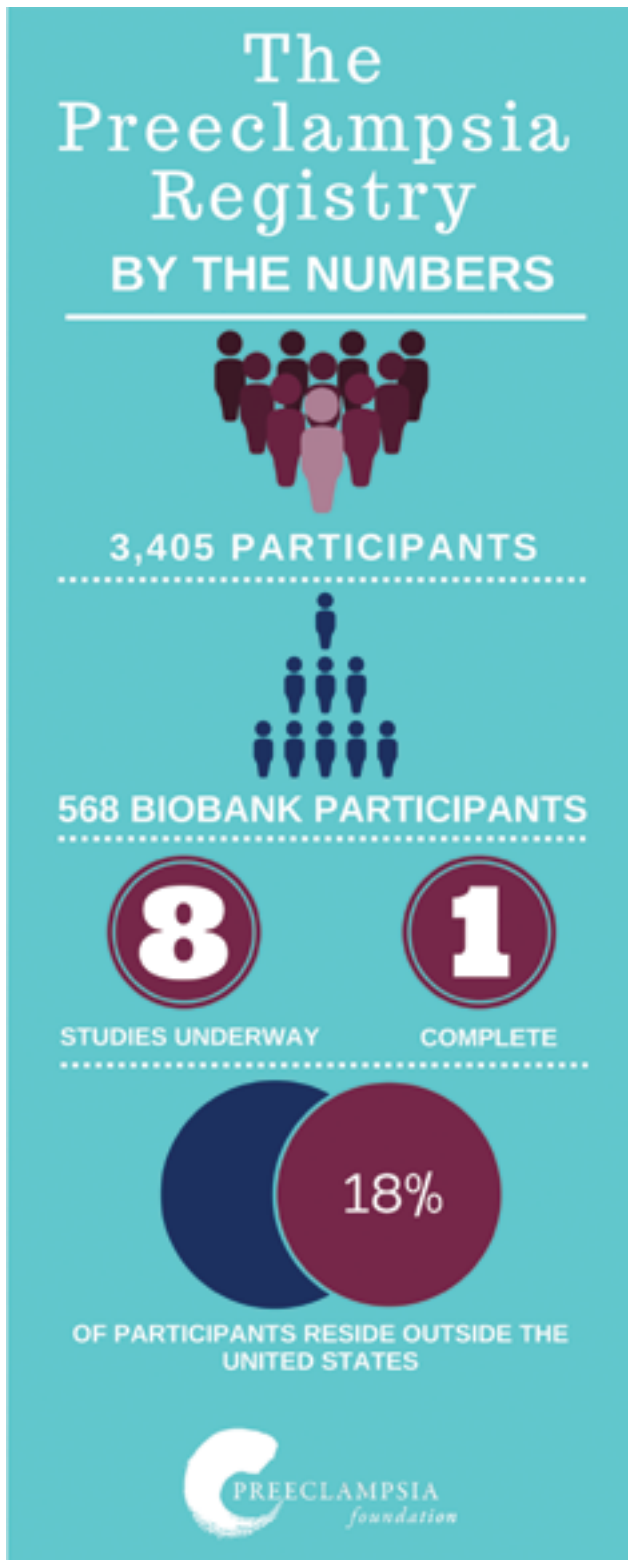


eliminate pre-eclampsia as a threat to mothers and their babies. A major component of this commitment—The Preeclampsia Registry—celebrates its fourth anniversary as a valuable resource for researchers. It now has more than 3,400 participants, 18 percent of whom reside outside the U.S., in this online patient and family database for those affected by pre-eclampsia and related hypertensive disorders of pregnancy. The Preeclampsia Registry participates in PRE-EMPT's Global Pregnancy Collaboration (CoLab), which is overseen by an Institutional Review Board and includes all the data variables recommended by CoLab.



ABOVE LEFT: Mansion House in Dublin was lit up in orange to bring attention to the first ever World Preeclampsia Day on May 22 2017.

ABOVE RIGHT: The NZAPEC team spent World Preeclampsia Day visiting midwifery practices and schools in Christchurch and Auckland.



The Preeclampsia Foundation continues to fund research through its Vision Grants and EMPOWER program (Empowering Progress in Obstetric and Women’s hEalth Research). EMPOWER creates and supports partnerships between seasoned mentors and young investigators to improve research capacity in low-resource settings. Last year, the second award was granted to a pre-eclampsia researcher from a low- to middle-income country through EMPOWER, in partnership with ISSHP, PRE-EMPT/CoLab, and supporting organisation New Zealand Action on Pre-eclampsia.

### Year 8 Deliverables

The Preeclampsia Foundation will continue to work to enhance patient advocacy and education, including expanding The Preeclampsia Registry to enroll diverse populations. Efforts to expand our reach to Spanish-speaking populations is underway, with a renewed focus on the Foundation’s Spanish website and social media outreach.

# GLOWM Safer Motherhood App Resource for Mobile Phones

The GLOWM Safer Motherhood APP is unique in that it provides midwives (and other medical personnel) not only with an extensive range practical guidance on the management of obstetric emergencies but also offers them the option of storing their patient records securely on their phones and sharing these records with their



clinics. The programme was developed at the request of the WHO (African Region) and it has now been widely tested and evaluated throughout Africa and Asia.

The clinical resources that are available include short animated videos on managing many childbirth-related conditions including pre-eclampsia, PPH and maternal sepsis and skills videos on many obstetric topics including breech delivery, shoulder dystocia and neonatal resuscitation. In addition, it also features tutorials, educational films, community education items and even some short textbooks. It is a feature of the APP that new resources can be added at any time and existing resources updated remotely.

The special medical records module serves firstly to remind the midwife of all the checks that should be undertaken at each stage of pregnancy and childbirth and secondly, is an easy way of recording the results of each examination quickly and permanently. Because these records can be readily shared with the midwife's clinic or hospital, it is hoped that they will help supervising authorities assemble useful data as well as monitoring individual patient care.

The Global Library of Women's Medicine (GLOWM) has recently launched the APP and it is now available for anyone to download FREE. The APP can be viewed in full—and actually tested—at [www.glowm.com/mobile/app](http://www.glowm.com/mobile/app). Currently, it is available for android phones (and tablets) only but during September it will also become available for iPhones (and i-tablets) as well.



ABOVE TOP LEFT: Midwives participate in the Safer Motherhood App training in Botswana.

ABOVE BOTTOM LEFT: Safer Motherhood App.

# Magnesium Sulphate for Fetal Neuroprotection of the Preterm Infant (MAG-CP)

**PI:** Laura A. Magee and Anne Synnes

**Trainee (co-ordinator):** Dane A. De Silva (Master in Public Health)

**Funding:** Canadian Institutes for Health Research; BC Women's Hospital; NeuroDevNet

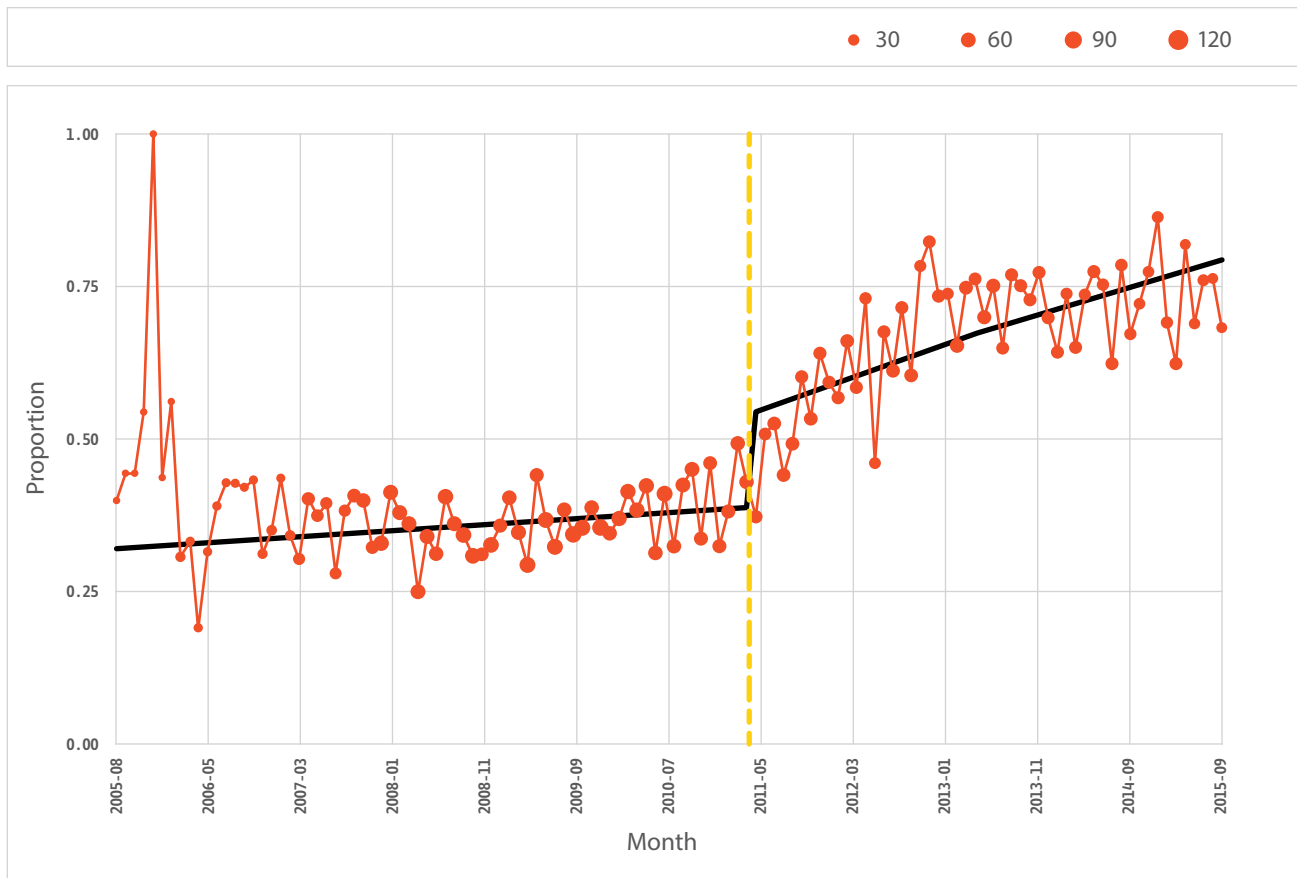
The Canadian Perinatal Network (CPN) is a network of tertiary centres that aims to improve care of high-risk women and infants born very preterm. Its current focus is on the national managed knowledge translation (KT) project, MAG-CP, jointly led by CPN (LA Magee) and the Canadian Neonatal Follow-Up Network (CNFUN) (A Synnes). MAG-CP was born from relevant trials and meta-analyses that recommended use of  $MgSO_4$  for fetal neuroprotection of the preterm infant to prevent cerebral palsy. This led to the 2011 Society of Obstetricians and Gynaecologists of Canada (SOGC) Clinical Practice Guidelines, which MAG-CP aimed to translate into clinical practice by engaging health care professionals through a process of active KT.

The KT intervention of the MAG-CP project consisted of four parts: (1) initiating and leading a SOGC clinical practice guideline, published in May 2011; and then from 2011-15 (2) an e-learning module; (3) a 'Barriers & Facilitators Survey'; and (4) site visits and other interactive activities between the central MAG-CP team and individual sites. The first two components of the KT were available to all practitioners in Canada, while the third and fourth components were delivered to practitioners at participating sites in the CPN. Other activities undertaken included a monthly newsletter, monthly teleconferences, supportive emails and one-on-one support for questions and advice, provision of KT tools (such as pre-printed physician orders, presentation materials, information sheets for staff and women, and reminders for women who were being expectantly managed in hospital and at risk of preterm birth at <32 weeks. Bi-annual site-specific reports on  $MgSO_4$  for fetal neuroprotection use that compared each site with activity overall were prepared in order to create an audit cycle to inform and fuel ongoing KT. Sites were asked to track their KT activity using a web-based form for participation and conducting these activities.



MAG-CP tracked pregnancies at high-risk of very preterm birth at <29 weeks, and audited magnesium sulphate use in threatened and imminent preterm birth, including monitoring maternal and perinatal outcomes before the KT intervention (Aug 2005 – May 2011) and during the intervention (Jun 2011 – Sept 2015). The primary outcome was optimal use of magnesium sulphate over time to a pre-specified goal of 80%, while the secondary outcome was cerebral palsy or 'death or cerebral palsy'. 'Other' outcomes specified a priori were maternal safety (including hypotension) and newborn safety (including resuscitation).

Canadian tertiary centres contributed data on 7,888 women, with 4,745 women pre-KT (18 centres), and 3,143 during the intervention (11 centres). The KT intervention was associated with: an 84% increase in the odds of optimal use (OR 1.00 to 1.84,  $p < 0.001$ ), after which there was a continuous increase of 2% per month, representing an overall increase of 220% compared to the pre-KT era. The intervention was also associated with a reduction in the odds of underuse (OR 1.00 to 0.47,  $p < 0.001$ ), and an increase in suboptimal use (use that was too early or at  $\geq 32$  weeks) (1.18 to 2.18,  $p < 0.001$ ). Maternal hypotension was uncommon (7/1,512, 0.5%). Nationally, intensive neonatal resuscitation decreased ( $p = 0.024$ ) despite rising  $MgSO_4$  use for fetal



neuroprotection ( $p < 0.001$ ). Death or cerebral palsy rates of these infants will be determined at the two-year follow-up through the Canadian Neonatal Follow-Up Network (CNFUN).

## Publications

Publications have included a cost-effectiveness analysis of magnesium sulphate for fetal neuroprotection (BMC Pregnancy Childbirth 2014), a systematic review of the impact of magnesium sulphate on fetal heart rate and pattern (JOGC 2014), analysis of the various KT strategies (BMC Pregnancy Childbirth 2015), and variability in magnesium sulphate protocols between Canadian perinatal centres (JOGC 2015). The primary results for MAG-CP are currently under review with Implementation Science. Preliminary results have been presented locally at Obstetric and Paediatric Grand Rounds, nationally at the Canadian National Perinatal Research Meeting, and

internationally at the Royal College of Obstetricians & Gynaecologists Congress.

## Presentations

- De Silva DA, Synnes AR, von Dadelszen P et al. for the MAG-CP & CNN Collaborative groups. MAGnesium sulphate for fetal neuroprotection to prevent Cerebral Palsy (MAG-CP)—a managed knowledge translation project to implement guidelines in Canada. Canadian National Perinatal Research Meeting, February 2017, Montebello, CA (oral presenter).
- De Silva DA, Synnes AR, von Dadelszen P et al. for the MAG-CP & CNN Collaborative groups. MAGnesium sulphate for fetal neuroprotection to prevent Cerebral Palsy (MAG-CP)—a managed knowledge translation project to implement guidelines in Canada. Royal College of Obstetricians and Gynaecologists (RCOG) World Congress, March 2017, Cape Town, ZA. BJOG 2017; 124:70 (poster presenter).

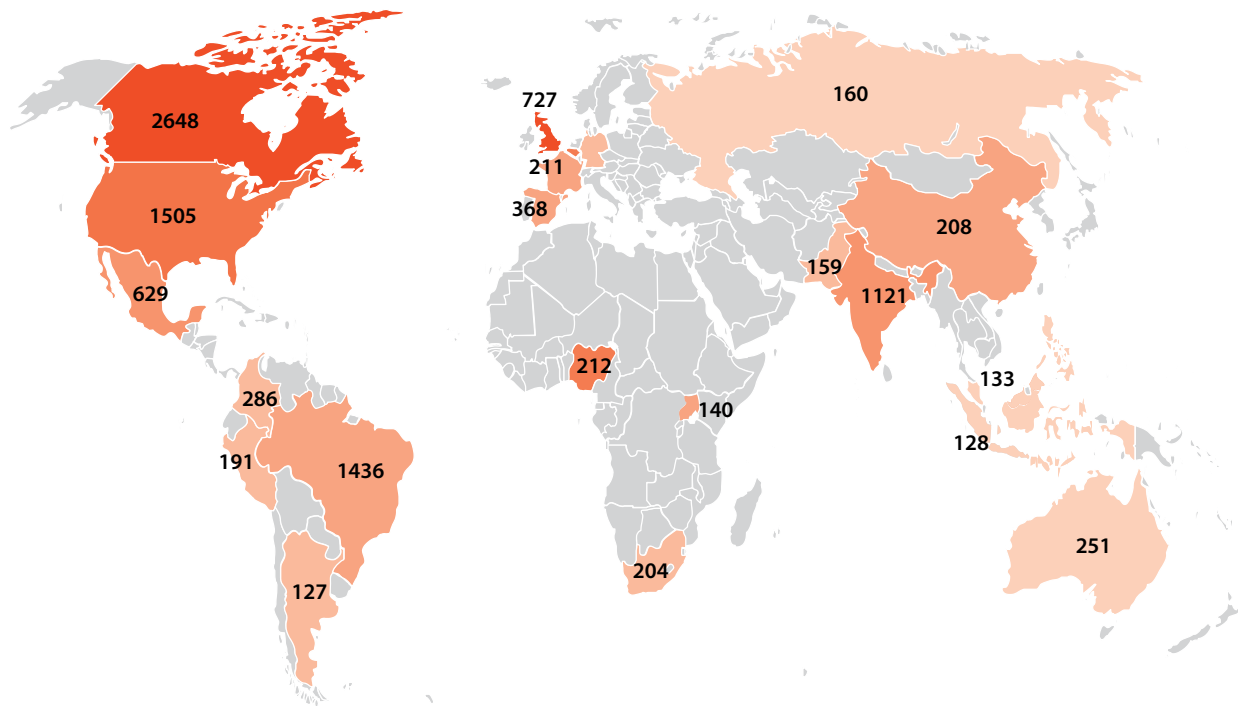
ABOVE: Segmented regression analysis of optimal use of  $MgSO_4$  during pre-MAG-CP (2005-11) and MAG-CP (2011-15) eras. The dashed line indicates implementation of the KT intervention.

# PRE-EMPT Advocacy, Global Access and Select Publications

PRE-EMPT has used multiple strategies to advocate at national and international levels for improved awareness and outcomes related to pre-eclampsia and eclampsia. We continue to use the PRE-EMPT website (<https://pre-empt.bchr.ca/>) as the primary platform for the dissemination of study updates. We are proud to have website visitors from a wide-range of countries, please see the map below for the top visitors by country.

PRE-EMPT continues to be active on social media, particularly twitter (@UBCPREEMPT), where this year we received the most impressions of any one tweet. The following tweet results in 22,328 impressions!

#Preeclampsia is a preventable and inexpensive disease to treat, yet it is the second leading cause of maternal death #WorldPreeclampsiaDay



# Joint ISSHP/ISOM Global Health Committee

## Overview

The joint International Society of Obstetric Medicine (ISOM) and International Society for the Study of Hypertension in Pregnancy (ISSHP) Global Health Committee aims to promote best clinical, research, and advocacy practices by relevant stakeholders in under-resourced settings through their existing systems. The ultimate goal is to build capacity and to improve outcomes for women and their babies wherever they live.

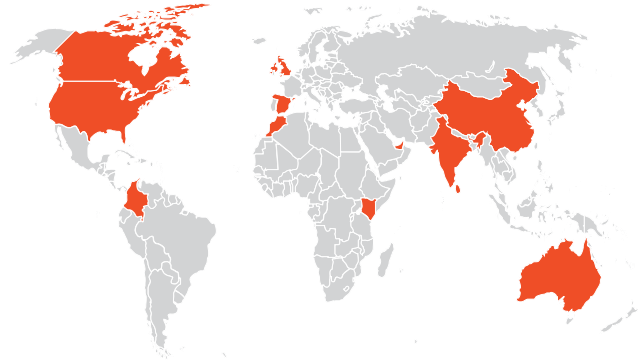
The joint International Society of Obstetric Medicine (ISOM) and International Society for the Study of Hypertension in Pregnancy (ISSHP) Global Health Committee was established following the 2014 ISOM/ISSHP meetings in New Orleans, USA, where it was emphasised that these organisations need a global perspective to address maternal death and disability, the vast majority of which occurs in under-resourced settings.

The Global Health Committee consists of twenty-five representatives from both ISSHP and ISOM. Committee members are clinicians and researchers from well- and under-resourced settings and from various disciplines, including obstetric internal medicine, anaesthesia, obstetrics and gynaecology (including maternal-fetal medicine), public health, and discovery science.

The committee membership has grown since the publishing of the last annual reports and now includes new representatives from Colombia (3), UAE (1), Morocco (1), Canada (2), India (1). The full membership list of the committee can be accessed in Appendix A.

## Year 7 Progress

Over the last year, the committee members have been actively engaged in various activities including conducting a second round of global obstetric medicine needs survey, developing a list of maternal health/obstetric medicine summaries for the WHO Reproductive Health Library,



and publishing a series on the models of obstetric care in different regions of the world (in *Obstetric Medicine*, March 2017. Volume 10:1. pp. 3–47).

In October 2016 at the XXI World Congress, the Joint ISSHP and ISOM Global Health Committee held a global health symposium with the aim of engaging the delegates and identifying how the committee could work to promote the best clinical, research, and advocacy practices in under-resourced settings. Emerging from this discussion was the need for support and training for emergency obstetric care in under resourced setting and the need to strengthen capacity for robust basic science research, particularly to understand the pathophysiology of pre-eclampsia in diverse populations.

## Year 8 Deliverables

- Establishing a presence at international meetings by organising symposiums and workshops
- Collaborating and networking with professional organisations
- Development of educational modules for health care providers in low and middle income countries

ABOVE RIGHT: The above figure shows the countries (in orange) where the members of the ISSHP and ISOM Global Health Committee are based.

## Notable Awards

- Tom Easterling wins the International Society for the Study of Hypertension in Pregnancy's Chesley Award for his sustained and substantial contribution to research in pre-eclampsia.
- Congratulations to Beth Payne who was awarded a highly coveted Postdoctoral Fellowship from the Canadian Institutes of Health Research (CIHR) in 2016. This two-year fellowship with focus on "Building the gap: from research to sustainable implementation of a mobile health tool in a low-resourced setting". This award will support Beth's salary while she leads a study to determine the health worker and health system stakeholder's perspectives on the impact and acceptability of the PIERS on the Move mobile health application used in the CLIP Trial.
- Asif Khowaja received "Rising Star-2017" award from Vancouver Coastal Health Research Institute
- Hannah Nathan was the recipient of the Young Investigator Award for international oral presentation, RCOG World Congress, Cape Town, South Africa, Mar '17 (A prospective multi-centre study in South Africa evaluating the diagnostic accuracy of the Microlife CRADLE Vital Signs Alert to predict adverse outcomes in pre-eclampsia)
- Winner of Expert Opinions in Obstetrics and Gynaecology category for international oral presentation (Hannah Nathan), RCOG World Congress, Cape Town, South Africa, Mar '17 (Shock Index Trajectory in Untreated Obstetric Hypovolaemic Shock)
- Best poster presentation (Hannah Nathan), Global Women's Health Research Society Conference, Manchester (Development of a novel vital signs device to detect pre-eclampsia and obstetric shock in low-resource settings: the CRADLE Vital Signs Alert)
- In May 2017, PRE-EMPT Research Manager Marianne Vidler, was awarded her PhD from the Department of Reproductive and Developmental Science at the University of British Columbia.
- Tabassum was appointed as an attending physician in obstetric medicine at Brown University. She also earned a master's degree in Global Health Policy at the London School of Hygiene and Tropical Medicine.
- Tatenda completed his PhD in Geography from Simon Fraser University and rejoined the Midlands State University in Zimbabwe as a Lecturer.

## Scientific Community

Over 35 peer-reviewed articles have been published in high-impact journals by PRE-EMPT in 2016-17, these are outlined by project in this report. Open-access continues to be a top priority for the team, and all publications have been made freely available to all.

## Industry Collaboration

PRE-EMPT has continued collaboration with industry to foster innovation in global health, and to develop and share new knowledge and expertise.

Our most notable partnerships include:

- **LionsGate Technologies:** A partnership with LionsGate Technologies has led to the development of the Phone Oximeter. This novel tool has been used in the CLIP Trials in Mozambique and Pakistan.
- **Microlife:** The long-standing collaboration between the King's College London CRADLE research group and Microlife has resulted in the development and evaluation of the Microlife CRADLE Vital Signs Alert (VSA), a device that measures blood pressure and pulse for use in pregnancy in low- and middle-income countries. It can be manufactured at low cost (<\$25/piece). The CRADLE VSA and its prototype (Microlife 3AS1-2 device) were used in the CLIP Trial.
- **LifeAssay Diagnostics:** PRE-EMPT's CoLab, LifeAssay Diagnostics, and PATH have partnered up together develop a low-cost urine protein/creatinine dipstick for screening for pre-eclampsia. The protein:creatinine values will be used as a gold standard for evaluation of the LifeAssay dipstick compared with commercially available dipsticks.

The predictive values for pre-eclampsia will also be compared between the various methodologies, using the clinical data from the CAP Study.

- **Roche Diagnostics:** CoLab is working with Dr. Leandro Oliveira who has received funding from Roche Diagnostics for a study using samples from the PrePARE biorepository. The study addresses the potential usefulness of PLGF to stratify risk in apparently low-risk women at 28 to 32 weeks of gestation.
- **Metabolomic Diagnostics Ltd:** CoLab recently provided a letter of support to collaborate with Metabolomic Diagnostics Ltd on PRESEDE: PREgnancy Screening offers Early DETection of Preeclampsia Risk, a study of diagnostic screening tests for pre-eclampsia that they are developing.
- **Alere:** One of the inclusion criteria for the STRIDER Canada trial is measuring the Placental Growth Factor (PLGF) levels. The PLGF is a biomarker that would differentiate whether fetus is placentally or constitutionally small for gestational age. The STRIDER team has fostered collaboration with Alere, a manufacturer of PLGF testing kit. Alere will be providing the PLGF test kit and MeterPro for all the STRIDER Canada participating sites.
- **Maternova:** Maternova assists in the distribution of the CRADLE VSA to low- and middle-income countries. The device can also be purchased directly from the CRADLE team at KCL.
- The CLIP Trial has received support from additional companies such as Karbonn Mobile, and Dell Canada.
- The CLIP Trial has had a rewarding partnership with graphic designer, Natsuko Hayashida, who has designed many crucial parts of the CLIP intervention including pictograms used.

## Partnerships

### **World Health Organization Department of Maternal, Newborn, Child and Adolescent Health (MNCAH)**

The MNCAH group was instrumental in coordinating the development of the 2011 WHO pre-eclampsia guidelines,

and will be instrumental in supporting the dissemination of PRE-EMPT results.

### **UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (RHR)**

The WHO RHR group has been important partner in the PIERS research agenda (Mario Merialdi and Mariana Widmer), as well as for Objectives 1 (Ana Pilar Bertràn) and 5 (Metin Gülmezoglu) of the PRE-EMPT project.

### **Royal College of Obstetricians and Gynaecologists (RCOG)**

We have developed a partnership with the RCOG (London) International Office. An element of the RCOG's international mandate is to strengthen the capacity of inpatient facilities in LMICs in terms of the use of evidence-based care.

### **Jhpiego/ MCSP (Maternal Child Survival Program)**

PRE-EMPT has developed a partnership with MCHIP and now the MCSP, particularly through Jeffrey Smith (PRE-EMPT TAG member).

### **Ending Eclampsia**

Ending Eclampsia is a project that from the Population Council that has been spear headed by Charlotte Warren, PRE-EMPT TAG member. PRE-EMPT has been in active sharing resources with Ending Eclampsia. Laura Magee (co-chair of Objective 3) has engaged with the project through participation at the 'An Unfinished Agenda in Maternal Health: Meeting the Needs of Women with Preeclampsia/Eclampsia and Postpartum Hemorrhage' in Washington DC on June 13 2017. In addition, Charlotte Warren provided critical guidance and support to the CLIP team through participation at a site visit in January 2016.

### **Clinton Health Access Initiative (CHAI)**

In Mozambique, PRE-EMPT has partnered up with the CHAI in-country team members, working alongside Beatriz Manriquez Rocha and Lise Ellyin, on the identification of women at risk of complications on pre-eclampsia.

## **PATH**

The CAP Study has partnered up with PATH to develop a low-cost urine protein/creatinine dipstick for screening for pre-eclampsia. Through research and development, we are aiming to create a commercially available dipstick that will be the gold standard for the evaluation of pre-eclampsia.

## **GLOWM Safer Motherhood & D-Tree International**

Partnering with the GLOWM Safer Motherhood group and D-Tree International, Dr Beth Payne has been seeking funding to support implementation of an integrated maternal mobile health platform. This platform combines GLOWM's health worker education and training materials, D-Tree's ePartogram and validated prediction models, such as miniPIERS to support decision making by health workers during antenatal, intrapartum and postpartum care. All of these components are integrated into a dynamic eHealth record for use in primary health and referral centres. The overall aim is to support quality of care improvements across the continuum of pregnancy to ensure all mothers get the right care at the right time.

## **CAP Partner Institutions**

- World Health Organization
- South Africa
  - + East London Hospital Complex
  - + University of Fort Hare
  - + University of the Witwatersand
  - + University of Cape Town
  - + Stellenbosch University
- Zimbabwe
  - + University of Zimbabwe
- Argentina
  - + Hospital Italiano de San Justo Agustín Rocca
  - + CEMIC
  - + Hospital Italiano de Buenos Aires
  - + Instituto de Efectividad Clínica Sanitaria (IECS)

## **miniPIERS Partner Institutions**

- Pakistan
  - + Aga Khan University
  - + Jinnah Postgraduate Medical College
- South Africa
  - + Stellenbosch University
- Fiji
  - + University of Fiji
- Brazil
  - + UNIFESP
- Uganda
  - + Makerere University
- World Health Organization

## **Maternal Mortality & Morbidity Working Group**

### **Partners**

- World Health Organization RHR

### **PIERS on the Move Partner Institutions**

- South Africa
  - + Stellenbosch University
  - + East London Health Complex

### **MOM Partner Institutions**

- Canada
  - + Simon Fraser University
- Mozambique
  - + Manhiça Health Research Centre
- Zimbabwe
  - + University of Zimbabwe

### fullPIERS Partner Institutions

- Canada
  - + University of British Columbia
  - + University of Ottawa
  - + Université de Sherbrooke
- United Kingdom
  - + University of Nottingham
  - + University of Leeds
  - + St. George's, University of London
- New Zealand
  - + Christchurch School of Medicine, University of Otago
- Australia
  - University of Western Australia

### CRADLE Partner Institutions

- South Africa
  - + Stellenbosch University
  - + University of Cape Town
- Zimbabwe
  - + University of Zimbabwe
- India
  - + Jawaharlal Nehru Medical College

### CLIP Partner Institutions

- Nigeria
  - + Centre for Research in Reproductive Health
  - + Olabisi Onabanjo University Teaching Hospital
- Mozambique
  - + Eduardo Mondlane University
  - + Centro de Investigação em Saúde de Manhiça
- Pakistan
  - + Aga Khan University
  - + Jinnah Postgraduate Medical College



- India
  - + Jawaharlal Nehru Medical College
  - + S Nijalingappa Medical College

### MAG-CP Partner Institutions

- Canada
  - + BC Women's Hospital
  - + Royal Alexandra Hospital
  - + Royal University Hospital
  - + London Health Sciences Centre
  - + Mount Sinai Hospital
  - + The Ottawa Hospital
  - + Centre Hospitalier de L'Université Laval
  - + IWK Health Centre, Halifax, NS
  - + Women's Health Clinic (Eastern Health)
  - + Centre Hospitalier Universitaire Sainte-Justine
  - + Dr. Everett Chalmers Hospital
  - + The Moncton Hospital

ABOVE RIGHT: Dane De Silva (MAG-CP co-ordinator) and Tang Lee (MAG-CP data analyst) participate in a teleconference with partner institutions.



ABOVE: Members of the PRE-EMPT Technical Advisory Group (Matthews Mathai, Eleni Tsigas, Laura Magee).

# Appendix



# Steering Committee Members

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## PRE-EMPT Management Committee

- Jerker Liljestrand, Bill & Melinda Gates Foundation
- Peter von Dadelszen, Kings College London
- **Vice Chair:** Marianne Vidler, University of British Columbia
- **Members:** Jim Roberts and Nicole Sirivansanti

## Objective Chairs and Vice Chairs

- Justus Hofmeyr
- Mandisa Singata
- Stephen Munjanja
- Beth Payne
- Zulfiqar Bhutta
- Laura Magee
- Jim Roberts
- Chris Redman
- Eleni Tsigas
- Matthews Mathai

## Technical Advisory Group

- Wame Baravilala
- Zulfiqar Bhutta
- Simone Diniz
- Robert Goldenberg
- Michael Gravett
- Simon Lewin
- Lucilla Poston
- Shuchita Mundle
- Olufemi Oladapo
- Laura Reichenbach
- Donna Russell
- Jeffrey Smith
- Eleni Tsigas
- Jimmy Walker
- Charlotte Warren
- Beverly Winikoff
- France Donnay
- Mark Brown
- Metin Gülmezoglu
- Cyril Engmann
- Gwyneth Lewis

## CAP Study

<b>Justus Hofmeyr</b>	University of Fort Hare and Witwatersrand University, South Africa
<b>Stephen Munjanja</b>	University of Zimbabwe, Zimbabwe
<b>Mandisa Singata</b>	University of Fort Hare and Witwatersrand University, South Africa
<b>José Belizán</b>	Institute of Clinical Effectiveness and Health Policy, Argentina
<b>Eduardo Bergel</b>	Institute of Clinical Effectiveness and Health Policy, Argentina
<b>Ana Pilar Betrán</b>	World Health Organization, Switzerland
<b>Armando Seuc</b>	World Health Organization, Switzerland
<b>Sarah Manyame</b>	University of Zimbabwe, Zimbabwe
<b>Sue Fawcus</b>	University of Cape Town, South Africa
<b>Natalia Novikova</b>	University of Fort Hare and Witwatersrand University, South Africa
<b>Simpiwe Mose</b>	University of Witwatersrand, South Africa
<b>David Hall</b>	University of Stellenbosch, South Africa
<b>Gabriela Cormick</b>	Institute of Clinical Effectiveness and Health Policy, Argentina
<b>Jim Roberts</b>	University of Pittsburgh/Magee-Womens Research Institute, USA
<b>Peter von Dadeslzen</b>	King's College London, UK
<b>Alvaro Ciganda</b>	Institute of Clinical Effectiveness and Health Policy, Argentina

## miniPIERS

<b>Beth Payne</b>	University of British Columbia, Canada
<b>Jennifer Hutcheon</b>	University of British Columbia, Canada
<b>Mark Ansermino</b>	University of British Columbia, Canada
<b>David Hall</b>	Stellenbosch University and Tygerberg Hospital, South Africa
<b>Shereen Bhutta</b>	Jinnah Post-graduate Medical College, Pakistan
<b>Christine Biryabarema</b>	Makerere University, Uganda
<b>William Grobman</b>	Feinberg School of Medicine Northwestern University, USA
<b>Henk Groen</b>	University Medical Center Groningen, University of Groningen, Netherlands
the late <b>Farizah Haniff</b>	Colonial War Memorial Hospital, Fiji

<b>Jing Li</b>	University of British Columbia, Canada
<b>Laura Magee</b>	King's College London, UK
<b>Mario Meriardi</b>	UNDP/UNFPA/WHO/World Bank Special Programme of Research, Switzerland
<b>Annetee Nakimuli</b>	Makerere University, Uganda
<b>Ziguang Qu</b>	University of British Columbia, Canada
<b>Rozina Sikandar</b>	Aga Khan University, Pakistan
<b>Nelson Sass</b>	Universidade Federal de São Paulo, Brazil
<b>Wilhelm Steyn</b>	Stellenbosch University and Tygerberg Hospital, South Africa
<b>Mariana Widmer</b>	UNDP/UNFPA/WHO/World Bank Special Programme of Research, Switzerland
<b>Jian Zhou</b>	Tongji University, P.R. China
<b>Peter von Dadelszen</b>	King's College London, UK

## CLIP Executive Committee

<b>Olalekan Adetoro</b>	Olabisi Onabanjo University Teaching Hospital, Nigeria
<b>Zulfiqar Bhutta</b>	Aga Khan University Medical Center, Pakistan
<b>Mrutyunjaya Bellad</b>	KLE University, India
<b>Shivaprasad Goudar</b>	KLE University, India
<b>Laura Magee</b>	Kings College London, UK
<b>Ashalata Mallapur</b>	KLE University, India
<b>Beth Payne</b>	University of British Columbia, Canada
<b>Rahat Qureshi</b>	Aga Khan University Medical Center, Pakistan
<b>John Obafemi Sotunsa</b>	Olabisi Onabanjo University Teaching Hospital, Nigeria
<b>Sumedha Sharma</b>	University of British Columbia, Canada
<b>Peter von Dadelszen</b>	Kings College London, UK

## CLIP Steering Committee

<b>Mark Ansermino</b>	University of British Columbia, Canada
<b>Ana Pilar Betran</b>	World Health Organization, Switzerland
<b>Guy Dumont</b>	University of British Columbia, Canada

<b>Susheela M. Engelbrecht</b>	Jhpiego, USA
<b>Veronique Filippi</b>	London School of Hygiene and Tropical Medicine, UK
<b>Tabassum Firoz</b>	Brown University, USA
<b>William Grobman</b>	Northwestern University Medical School, USA
<b>Marian Knight</b>	University of Oxford, UK
<b>Ana Langer</b>	Harvard School of Public Health, USA
<b>Simon Lewin</b>	Norwegian Knowledge Centre for the Health Services, Norway
<b>Gwyneth Lewis</b>	University College London, UK
<b>Craig Mitton</b>	Vancouver Coastal Health Research Institute, Canada
<b>Nadine Schuurman</b>	Simon Fraser University, Canada
<b>Andrew Shennan</b>	Kings College London, UK
<b>Joel Singer</b>	University of British Columbia, Canada
<b>Jim Thornton</b>	Nottingham City Hospital, UK
<b>Sharla Drebit</b>	University of British Columbia, Canada
<b>Richard Derman</b>	Jefferson Medical College, USA
<b>Hubert Wong</b>	University of British Columbia, Canada
<b>France Donnay</b>	Tulane University, USA

## CoLab Steering Committee

<b>RCWIH Biobank</b>	<b>S. Lee Adamson</b> Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Canada
<b>AMANHI</b>	<b>Abdullah Baqui</b> Johns Hopkins Bloomberg School of Public Health, USA
	<b>Fyezah Jehan</b> The Aga Khan University, Pakistan
	<b>Sunil Sazawal</b> Johns Hopkins; Annamalai University, India
<b>Accra Ghana Cohort</b>	<b>Joyce Browne</b> University Medical Center Utrecht, Netherlands

<b>Ohio State Patient Cohort</b>	<b>Catalin S. Buhimschi</b> Ohio State University Wexner Medical Center, USA
<b>GenPE</b>	<b>Juan Pablo Casas</b> University College London, UK
<b>EVERREST</b>	<b>Anna David</b> Institute for Women's Health, University College London, UK
<b>Iberoamerican Adverse Pregnancy Network</b>	<b>Carlos Escudero</b> Universidad del Bio Bio, Chillan, Chile
<b>NIH/NICHD Placental Bank</b>	<b>Susan J. Fisher</b> University of California San Francisco, USA
<b>GAPPS-Global Alliance to Prevent Prematurity and Stillbirth</b>	<b>Michael G. Gravett</b> GAPPS, USA
<b>Lund Database</b>	<b>Stefan Hansson</b> Lund University, Lund, Sweden
<b>POUCH Study</b>	<b>Claudia Holzman</b> Michigan State University, USA
<b>PEPP-Prenatal Exposures and Preeclampsia Prevention Member of Executive Committee</b>	<b>Arun Jeyabalan</b> Magee-Womens Research Institute; University of Pittsburgh, USA
<b>INTERBIO 21<sup>st</sup></b> <b>INTERGROWTH 21<sup>st</sup></b>	<b>Stephen Kennedy</b> University of Oxford, UK
<b>RANDERS</b>	<b>Ulla Breth Knudsen</b> Aarhus University Hospital, Denmark
<b>FINNPEC and PREDO</b>	<b>Hannele Laivuori</b> University of Helsinki, Finland
<b>Avon Longitudinal Study of Parents and Children</b>	<b>Deborah A. Lawlor</b> School of Social and Community Medicine, University of Bristol, UK
<b>The Ontario Birth Study</b>	<b>Stephen Lye</b> Lunenfeld-Tanenbaum Research Institute; University of Toronto, Canada
<b>Life Codes</b>	<b>Thomas F McElrath</b> Brigham & Women's Hospital, Harvard University, USA
<b>The Norwegian Mother and Child Cohort-MoBa</b>	<b>Per Magnus</b> Norwegian Institute of Public Health, Norway

<b>LMIC Representative CAPS Study EMPOWER GRANT RECIPIENT</b>	<b>Sarah Manyame</b> Harare, Zimbabwe
<b>Oregon Placental Bank Member Executive Committee</b>	<b>Leslie Myatt</b> Oregon Health & Science University, USA
<b>SCOPE, BASELINE (Children of SCOPE) and IMPROVED Member Executive Committee</b>	<b>Jenny Myers</b> University of Manchester, UK
<b>Co-Investigator Member Executive Committee</b>	<b>Roberta Ness</b> University of Texas School of Public Health, USA
<b>PREPARE Study</b>	<b>Leandro Gustavo De Oliveira</b> São Paulo State University, Brazil
<b>Danish Birth Cohort</b>	<b>Jorn Olsen</b> Aarhus University, Denmark
<b>VIP Study UPBEAT Study Member Executive Committee</b>	<b>Lucilla Poston</b> King's College London, UK
<b>Co-Investigator Member Executive Committee Oxford Biobank</b>	<b>Christopher WG Redman</b> University of Oxford, UK
<b>Principal Investigator—CoLab Chair-Executive Committee Project Manager: Lee Rager <a href="mailto:srager@mwri.magee.edu">srager@mwri.magee.edu</a> Data Manager: Kasey Dickenson <a href="mailto:dickensonke2@mwri.magee.edu">dickensonke2@mwri.magee.edu</a></b>	<b>* James M. Roberts</b> Magee-Womens Research institute; University of Pittsburgh, USA
<b>Iowa Maternal Fetal Tissue Bank</b>	<b>Mark Santillan</b> University of Iowa, USA
<b>Pregnancy Outcomes Prediction Study</b>	<b>Gordon C S Smith</b> University of Cambridge, UK
<b>CHASE Biobank Member Executive Committee</b>	<b>Anne Cathrine Staff</b> University of Oslo and Oslo University Hospital, Norway
<b>Generation R</b>	<b>Eric A.P. Steegers</b> Erasmus University
<b>Mass General Biobank</b>	<b>Ravi Thadhani</b> Harvard Medical School, Massachusetts General Hospital, USA

<b>Preeclampsia Foundation Registry</b> <b>Principal Investigator:</b> The Preeclampsia Registry	<b>Eleni Z. Tsigas</b> Preeclampsia Foundation
<b>Principal Investigator:</b> PRE-EMPT Member Executive Committee	<b>* Peter von Dadelszen</b> King's College London, UK
<b>PRE-EMPT Manager</b>	<b>Marianne Vidler</b> University British Columbia, Canada
<b>Tri-HELLP</b>	<b>Melissa Wilson</b> Keck School of Medicine, USA
<b>Beijing Cohort</b>	<b>Yan-ling Wang</b> Chinese Academy of Sciences, China
<b>Epidemiology Division NIH/ NICHD</b>	<b>Cuilin Zhang</b> NICHD/National Institutes of Health (NIH), USA

## WHO KT Working Group

<b>Mattews Mathai</b>	
<b>Ahmet Metin Gülmezoglu</b>	WHO, Switzerland
<b>João Paulo Dias De Souza</b>	WHO, Switzerland
<b>Simon Lewin</b>	Norwegian Knowledge Centre for the Health Services; and Health Systems Research Unit, Medical Research Council of South Africa
<b>Jack Moodley</b>	University of Kwazulu Natal, South Africa
<b>Olufemi T. Oladapo</b>	WHO, Switzerland
<b>Annie Portela</b>	WHO, Switzerland
<b>Jim Roberts</b>	Magee-Women's Research Institute, USA
<b>Jeffrey Michael Smith</b>	MCHIP/Jhpiego, USA
<b>Eleni Tsigas</b>	Preeclampsia Foundation, USA





ABOVE: Jim Roberts (CoLab PI), Carmen Swanepoel, and Sarah Manyame (CoLab LMIC representative and EMPOWER grant recipient) meet at Stellenbosch University.

# Appendix



## CoLab Ongoing Research Projects

<b>CoLab Ongoing Research Projects</b>	
<b>Project Title</b>	<b>Investigators</b>
Variation in endoglin pathway genes associated with pre-eclampsia (Paper submitted and in review)	<b>PI:</b> Mandy Bell Schmella, PhD <b>Sponsor:</b> Carl Hubel, PhD
PREDO: Understanding, diagnosing and predicting pregnancy outcome in women with chronic hypertension (Paper submitted to BMJ Open May 2017)	<b>PI:</b> Lucy Chappell, MD <b>CoLab Co-Is:</b> Drs. Kate Bramham, Lucilla Poston and Hannele Laivuori
Biomarker assay development for translation of discovery-based placental mRNA candidates to serum protein concentrations in early pregnancy to predict pre-eclampsia	<b>PI:</b> Sandra Founds, PhD <b>Sponsor:</b> Jim Roberts, MD
Inflammatory profiling of pre-eclampsia, highlighting fetal gender, parity, BMI and IUGR: a case control study	<b>PI:</b> Maya Jalmbly, MD, PhD <b>Sponsor:</b> Stefan Hansson, MD
Maternal circulating angiogenic factors and subtypes of pre-eclampsia	<b>PI:</b> Annetine Staff, MD <b>CoLab Co-Investigators:</b> Drs Chris Redman, Peter von Dadelszen, Roberta Ness, Culin Zhang with Samantha Benton, Orlaith Burke and Pawel Szafranski
Sex specific differences in the placental syndrome and markers of placentation (Project completed and paper published—Plans for follow-up study)	<b>PI:</b> Dr. Sarah Schalekamp-Timmermans <b>Sponsor:</b> Prof. Dr. Eric Steegers
The fullPIERS risk prediction model: external validation and added value of a novel biomarker	Prof Peter von Dadelszen, MD Ugochinyere Vivian Ukah
Angiogenic factors in the identification of intrauterine growth restriction (Project completed)	Prof Peter von Dadelszen, MD Samantha Benton
The role of placental microparticles, Toll-like receptors and inflammation in PE. Awaiting funding	<b>PI:</b> Brandie DePaoli Taylor, PhD, MPH <b>Sponsor:</b> Jim Roberts, MD
The PREDICTV (Preeclampsia Early Determination for Intervention, Cure and Therapeutics by other Vasopressin) Study	<b>PI:</b> Mark Santillan, MD
Identification of molecular subclasses of pre-eclampsia.	<b>Co-PIs:</b> Shannon Bainbridge, PhD and Brian Cox, PhD <b>Sponsor:</b> Jim Roberts, MD
Prognostic value of Diamine Oxidase (DAO) levels in pre-eclampsia (Paper submitted April 2017)	Thomas Boehm, Martin Knoefler <b>Sponsor:</b> Leslie Myatt

### Projects Created During 2013 CoLab Oxford Meeting

Project Title	Investigators
Development of database to be made available to international research community for harmonization of PE research (COLLECT)	Profs Chris Redman, Les Myatt, Jenny Myers, Lucilla Poston, and Peter von Dadelszen in collaboration with MedSciNet Project Manager/Software Developer, Laima Juodvirsiene and colleagues
Reverse phenotype cluster analysis of TCA. Project Closed.	Profs Jenny Myers, Les Myatt, Lucilla Poston, Chris Redman, Annetine Staff
Regulatory and administrative institutional obstacles to collaborative research and sharing of biological data and samples. (Position Paper Published)	Profs Jim Roberts, Lucilla Poston, Roberta Ness and Deborah Mascalzoni

### Projects Created During 2014 CoLab Oxford Meeting

Project Title	Investigators
Preeclampsia and Later Life Cardiovascular Disease (Position Paper Published)	Staff AC, Redman CW, Williams D, Leeson P, Moe K, Thilaganathan B, Magnus P, Steegers EA, Tsigas EZ, Ness RB, Myatt L, Poston L, Roberts JM
Big Data—Potential power and problems for Preeclampsia research—CoLab role. Invitation to submit Brief Review to Hypertension. Submitted	Profs Les Myatt, Jim Roberts and Brady Bernard, Institute of Systems Biology
Projects Created During 2015 CoLab Oxford Meeting	
Reverse Phenotyping at time of disease	Profs Jenny Myers, Leslie Myatt, Jim Roberts, Roberta Ness and Lucilla Poston
Sisters and Daughters of Women with Preeclampsia (Seed Grant Award 2017)	Hilary S. Gammill, Roberta Ness, James M. Roberts, Eleni Tsigas, Alina Brewer; Kasey Dickenson; Ingrid Granne, Chris Redman
Publish 2015 CoLab Conference Proceedings, Symposium on Placental Health. (In Press)	Graham Burton, Lynn Cox, Stefan Hansson, Andrew Murray, Les Myatt, Chris Redman, Jim Roberts, Neil Sebire, Dionne Tannetta, Daniel Vaiman,

Placental Working Group	Neil Sebire, Donna Russell, Melissa Wilson, Mark Santillan, Anna David, Rebecca Spencer, Tom McElrath, Susan Fisher, Hannele Laivuori
Rare Placenta Procurement Registry	Rebecca Spencer, Mark Santillan, Susan Fisher, Melissa Wilson

### Projects Created During 2016 CoLab Oxford Meeting

Project Title	Investigators
Microparticle Proteomics as a Marker for Impending Preterm Birth.	Thomas McElrath
Maternal-fetal genomics to identify low frequency and rare variants contributing to pre-eclampsia risk.	Kathryn Gray <b>Sponsor:</b> Thomas McElrath
Developing an Very early Pregnancy and Pre-pregnancy Biorepository.	Mark Santillan and Thomas McElrath
In Addition to “Seed” Should We Also Be Considering “Soil” in the Genesis of Preeclampsia? (A study or pre and early pregnancy decidua).	Kirk Conrad <b>Sponsor:</b> Jim Roberts
Sex specific differences in maternal hemodynamic adaptation to pregnancy.	Sarah Schalekamp-Timmermans, Eric Steegers
Publish 2016 CoLab Conference Proceedings “Pregnancy and very early pregnancy antecedents of adverse pregnancy outcomes” (Submission June 2017, Placenta).	Graham Burton, Judith Cartwright, Kirk Conrad, Hilary Gammill, Jenny Myers, Paul Moss, Chris Redman, Jim Roberts, Andrew Sharkey, Regine Steegers-Theunissen

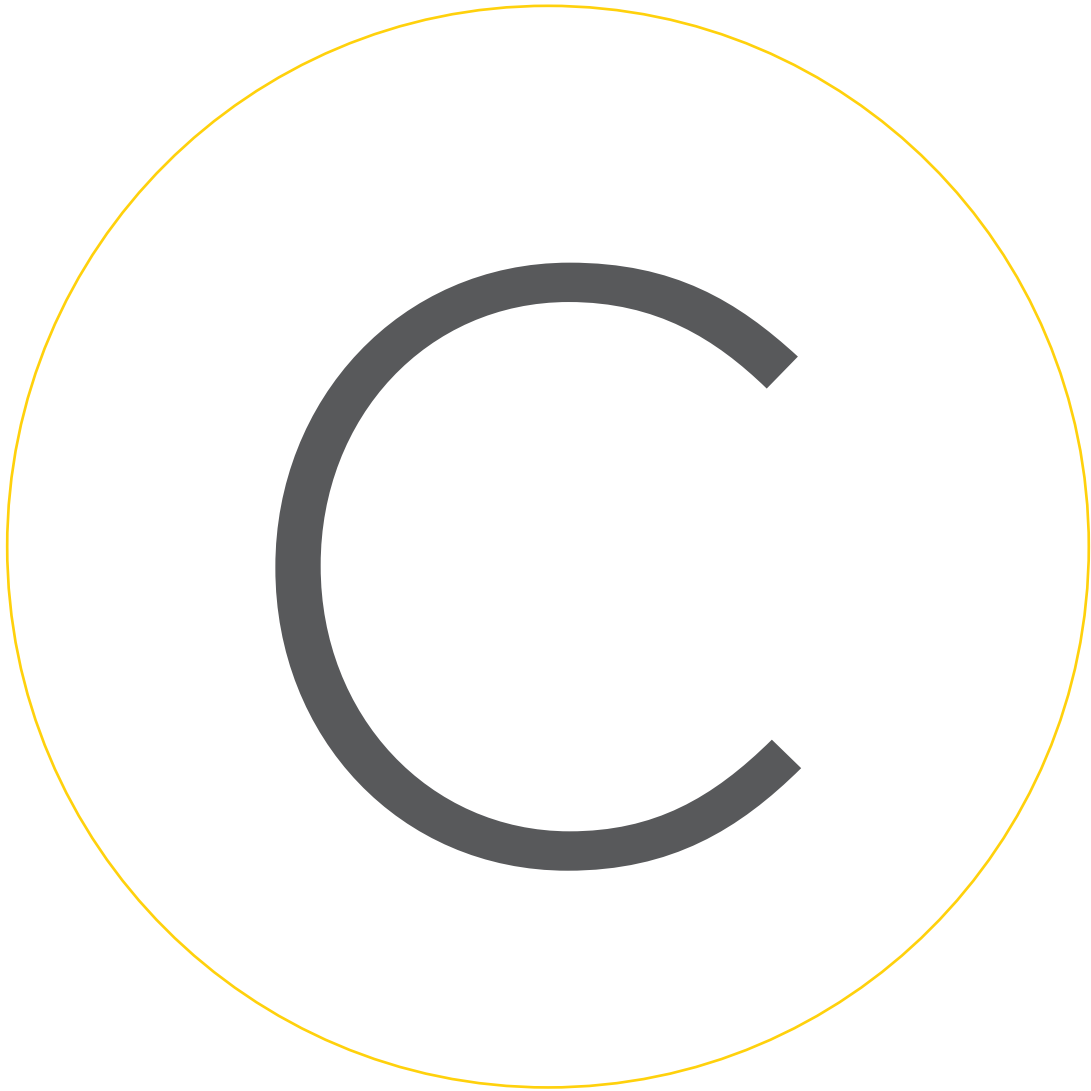


ABOVE: Lucilla Poston presents at the PRE-EMPT Annual Meeting 2014.



ABOVE: Tabassum Firoz, Joint ISSHP/ISOM Global Health Committee co-chair, at a community women's group in rural Bangladesh.

# Appendix



## Joint ISSHP/ISOM Global Health Committee

Name	Country
<b>Nelson Aguilar</b>	Colombia
<b>Bouchra Assarag</b>	Morocco
<b>Oier Ateka-Barrutia</b>	Spain
<b>Mark Brown</b> (ex officio)	Australia
<b>Kenneth Chen</b>	United States
<b>Peter von Dadelszen</b> (co-chair)	UK
<b>Eliana Castillo</b>	Canada
<b>Tony Duan</b>	China
<b>Thomas Easterling</b>	United States
<b>Tabassum Firoz</b> (co-chair)	United States
<b>Annemarie Hennessey</b>	Australia
<b>Louise Kenney</b>	Ireland
<b>Sandra Lowe</b> (ex officio)	Australia
<b>Laura Magee</b>	UK
<b>Nageena Mahmood</b>	UAE
<b>Shuchita Mundle</b>	India
<b>Omondi Ogutu</b>	Kenya
<b>Sunil T Pandaya</b>	India
<b>Jim Roberts</b>	United States
<b>Sumedha Sharma</b> (co-ordinator)	Canada
<b>Jose Antonio Rojas-Suarez</b>	Colombia
<b>Eleni Tsigas</b>	United States
<b>Mauricio Vasco</b>	Colombia
<b>Maria Escobar Vidarte</b>	Colombia
<b>Aahraz Wyne</b>	Canada
<b>Chandrika Wijeyaratne</b>	Sri Lanka



“... be sure that we have achieved much and that the impact of our work matters wherever women are most vulnerable to the maternal and perinatal risks associated with pregnancy hypertension and the placental disorders of pregnancy.”

—PETER VON DADELSZEN



**The University of British Columbia**

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