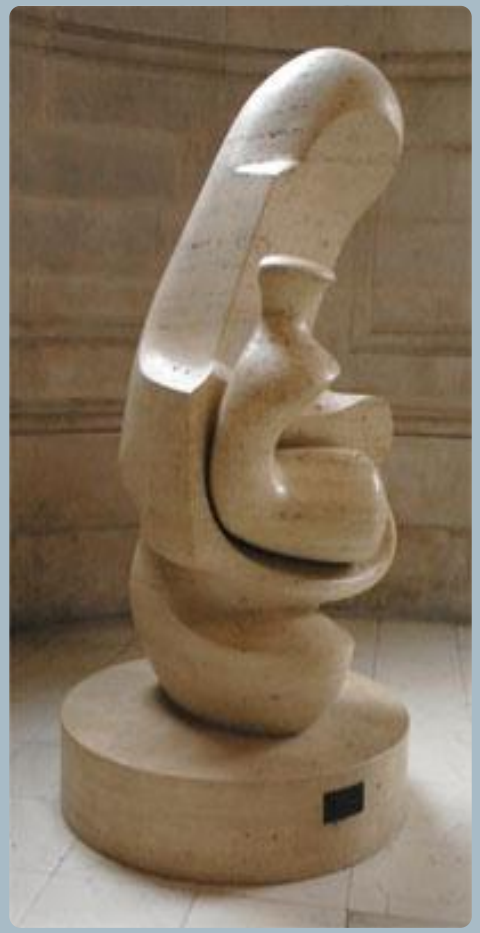

Technologies for Health Consultative Meeting: MNCH Pathways

Presented February 15–16, 2012

Updated March 15, 2012

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Preeclampsia/Eclampsia

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Support for this project is made possible by the generous support of the American people through the United States Agency for International Development (USAID) under the terms of the HealthTech Cooperative Agreement # AID-OAA-A-11-00051. The contents are the responsibility of PATH and do not necessarily reflect the views of USAID or the US Government.

Preventive Supplementation with Calcium

Reducing morbidity and mortality from preeclampsia/eclampsia (PE/E) requires primary prevention, and where that fails, timely identification and access to the treatment package for severe PE. Unfortunately, although 80 percent of pregnant women receive antenatal care at least once in low-resource countries, only slightly more than half receive the World Health Organization (WHO)-recommended minimum of four antenatal visits,[1] and consequently, do not have access to primary prevention interventions or screening for—or identification of—PE. Additionally, although most cases of eclampsia present in the third trimester of pregnancy, with about 80 percent of eclamptic seizures occurring intrapartum or within the first 48 hours following delivery, WHO reported in 2011 that only around 50 percent of deliveries were attended by skilled health personnel in the WHO Africa Region and the WHO South-East Asia Region,[1] making it impossible to treat seizures when they occurred.

Given the serious barriers to seeking and accessing obstetric services that currently exist, primary preventive interventions would reduce morbidity and mortality from PE/E in all pregnant women, but most significantly in those women who either might not receive treatment or receive it too late to prevent serious morbidity and mortality. WHO[2] recently recommended the following interventions for the prevention of PE: (1) in areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5 g–2.0 g elemental calcium per day) for all women, but especially those at high risk of developing PE/E (women with previous PE, diabetes, hypertension, renal disease, autoimmune disease, and multiple pregnancies); and (2) low-dose acetylsalicylic acid (aspirin, at doses of 75 mg) for women at high risk of developing the condition. While evidence-based primary prevention interventions currently exist, there is a clear need to find ways to increase access to them by ensuring they are relatively simple to administer, acceptable to pregnant women taking them, affordable, and easily available worldwide; can be integrated relatively easily into current logistics systems and existing programs; and are sustainable.

Calcium needs to be given to all pregnant women within the context of existing micronutrient supplementation programs and how to most effectively deliver all micronutrient supplementation needs to be determined. The long-standing program for pregnant women in most developing countries is iron-folic acid (IFA) supplementation (60 mg of iron and 400 mcg of folic acid), usually given combined in one pill to prevent anemia, from which half of all pregnant women in developing countries suffer. In the WHO recommendation for giving calcium daily to pregnant women, there was little guidance on how this supplement would be administered. It was acknowledged that iron and calcium compete for absorption and thus “concomitant administration of the two should be avoided.” This poses a problem for adherence. The extensive medical adherence literature suggests that adherence with a regimen is better when one rather than two or more medications are taken per day. Research on IFA supplementation in the early 1990s found that women were more likely to take one IFA supplement than separate iron and folic

acid pills.[3] This led to the availability of iron and folic acid in one combined tablet. Because it is not possible to add calcium to a tablet with iron without dramatically mitigating the absorption and dose of the iron, a new technology needs to be developed to decrease the competition between iron and calcium during absorption. This new product could reduce up to 30 percent of maternal deaths worldwide, if, as stated above, both demand and supply issues are addressed.

The following table investigates several types of calcium supplementation to prevent preeclampsia/eclampsia.

Supply Information	TECHNOLOGY/SOLUTION		
	Calcium tablets or powders	**Micronutrient powders for women (e.g., Sprinkles)**	**Heart bars**
Description	Calcium phosphate tablets (500 mg), or salt powder (in sachets) sprinkled on the main meal. A 1998 Cochrane review[4] showed (1) a large reduction in preeclampsia/eclampsia (PE/E) in several small studies; (2) no significant effect in a large US study; and (3) different effects in populations with low and adequate dietary calcium. A 2007 systematic review[5] showed that calcium supplementation during the second half of pregnancy decreased blood pressure, vascular tone, and serious complications related to hypertension. Huge discrepancies exist in the evidence and conclusions of the largest clinical trials.	Sprinkles are sachets (like small packets of sugar) that contain a blend of micronutrients in powder form. Sprinkles were developed for children and shown to be effective in reducing micronutrient deficiencies in children 6 months to 23 months. Any complementary, homemade food can be instantly fortified by adding Sprinkles. Coating of the iron prevents changes to the taste, color, and texture of the food to which Sprinkles is added. Similar products are being considered and piloted for pregnant women (by a number of groups), but these do not include large doses of calcium to prevent PE/E. SickKids is in the early stages of developing a supplement with iron, folic acid, and calcium (and possibly vitamin D) to prevent anemia and PE/E. This is a special formulation for pregnant and lactating mothers called Prenatal Sprinkles.	A food bar containing L-arginine and antioxidant vitamins. Two bars provide 6.6 g of L-arginine and antioxidant vitamins. Each bar weighs 35 g and contains 534 kJ (130 kcal).
Characteristics applicable for low-resource settings	Point of use. No need for power supply. No need for health care worker administration. Women need to take with water. The tablet is large in size, and some women may have difficulty taking the tablet without dividing it.	Point of use. No need for power supply. No need for health care worker administration. As a micronutrient powder, there is no need to take with water.	Point of use. No need for power supply. No need for health care worker administration.
Developer and/or manufacturer	Multiple, including Orion Laboratories Ltd, Bangladesh (calcium tablets).	Multiple, including the Sprinkles Global Health Initiative and the Hospital for Sick Children, Toronto, through its affiliate SickKids.	Current manufacturer unknown. Was previously manufactured by Nellson Nutraceutical, LLC (CA, USA).[6]

Supply Information	TECHNOLOGY/SOLUTION		
	Calcium tablets or powders	**Micronutrient powders for women (e.g., Sprinkles)**	**Heart bars**
Status	Commercialized. There is ongoing research to determine whether pre-pregnancy supplementation will reproduce the more dramatic epidemiological differences. In addition, there is research to determine if a lower dose of calcium would be effective. The Maternal & Child Health Integrated Program (MCHIP) tested the acceptability of calcium in two forms (tablets and powder) among pregnant women for three months in two village development committees of Banke district in southwestern Nepal. Results showed that women prefer calcium tablets over powder; and that on average, 98 percent would like to take calcium in the future. Based on this study, the Ministry of Health Family Health Division plans to scale up the findings through community-based volunteers in several districts. MCHIP will implement calcium supplementation district wide in one district, and other districts supported by different development partners. This project will demonstrate whether the government public health system, including female community health volunteers, can successfully distribute calcium for large-scale coverage and compliance.	A prenatal Sprinkles study in Bangladesh is planned to start 12 to 18 months from July 2011. Commercialization efforts are on hold. SickKids is exploring manufacturing and distribution partnerships in North America and in developing countries in both the private and public sectors.	Clinical. Conducted a randomized, blinded, placebo controlled clinical trial in a tertiary public hospital in Mexico City. Participants took two bars a day for five weeks.

Supply Information	TECHNOLOGY/SOLUTION		
	Calcium tablets or powders	**Micronutrient powders for women (e.g., Sprinkles)**	**Heart bars**
Efficacy/ effectiveness	Discrepancies in the evidence and conclusions of the largest clinical trials with high variability in realized benefits related to genetics and diet. Recent research derived from Cochrane review used 20 percent efficacy to model calcium effectiveness in lowering PE prevalence. This corresponds to 19 averted maternal deaths per 100,000 reached. Iron folate by contrast is 130 averted maternal deaths per 100,000 reached.[7]	Can potentially reduce maternal hypertensive disease-related mortality by 20 percent and preterm birth by 24 percent. Clinical trials in Ghana and other countries have shown that Sprinkles supplements are as efficacious in treating iron-deficiency anemia in infants as the standard treatment of oral iron drops.	Supplementation during pregnancy with a medical food containing L-arginine and antioxidant vitamins reduced the incidence of PE in a population at high risk of the condition. Antioxidant vitamins alone did not have a protective effect for prevention of PE. Supplementation with L-arginine plus antioxidant vitamins needs to be evaluated in a low-risk population to determine the generalizability of the protective effect, and the relative contributions of L-arginine and antioxidant vitamins to the observed effects of the combined treatment need to be determined.[8]
Manufacturing	No suppliers were identified with product of 1.5 g to 2.0 g dose. Currently, a 500-mg pill and sachets are available. Drug of adequate dose is not yet on UNICEF Essential Medicines List nor does UNICEF supply any product for this purpose.	Developed by researchers at the Hospital for Sick Children in Toronto. The Sprinkles Global Health Initiative is the nonprofit entity. Not yet commercially available.	Nellson Nutraceutical, LLC, has production facilities in Irwindale, California, and Salt Lake City, Utah, USA, and Montreal, Ontario, Canada. However, they are no longer manufacturing this product. The current manufacturer is unknown.
Intellectual property (IP) ownership	None. Generic product.	The IP rights to Sprinkles are owned by Ped Med, Ltd., a private incorporated company owned by Dr. Stanley Zlotkin.	Information not available.
Cost and cost drivers	Preliminary cost modeling suggests that the cost for a 1.5 g to 2.0 g dose of calcium at current pricing would be US$0.096 to US$0.15 per unit for calcium carbonate, US$0.264 to US$0.375 for calcium citrate, and US$0.021 to US$0.041 for a chewable calcium pill.[9] This does not compare favorably for example with iron-folic-acid pill (60 mg of ferrous fumarate) that costs US$5.34 per 1,000 or US$0.00534/each.	The cost of producing Sprinkles is between US$0.03 and US$0.05 per sachet, depending on the volume that is produced.	To be evaluated.
Delivery/ procurement channels	In the public sector, clinic- or community-based distribution. In the private sector, community-based distribution through private-sector vendors.	In the public sector, clinic- or community-based distribution. In the private sector, community-based distribution through private-sector vendors.	In the public sector, clinic- or community-based distribution. In the private sector, community-based distribution through private-sector vendors.
Sustainable business models	Currently, large multinational donors and ministries of health purchase the product. Private-sector distribution requires end users to be willing to pay for the product.	Business models not yet determined.	Not determined; US$1/day populations cannot afford unsubsidized, packaged food.

Demand Information	TECHNOLOGY/SOLUTION		
	Calcium tablets or powders	**Micronutrient powders for women (e.g., Sprinkles)**	**Heart bars**
Existing demand	Market size is driven by the number of pregnant women with low dietary intake of calcium (whether or not they have predisposing factors for preeclampsia [PE]). Broadly speaking, the market size for these technologies includes all pregnant women in countries where calcium deficiency is suspected to be prevalent.	Market size is driven by the number of pregnant women with low dietary intake of calcium (whether or not they have predisposing factors for PE). Broadly speaking, the market size for these technologies includes all pregnant women in countries where calcium deficiency is suspected to be prevalent.	Market size is driven by the number of pregnant women with low dietary intake of calcium (whether or not they have predisposing factors for PE). Broadly speaking, the market size for these technologies includes all pregnant women in countries where calcium deficiency is suspected to be prevalent.
Attractiveness	Widely available. Tablet form preferred. Iron and calcium cannot be taken together, so it complicates administration of both.	The powder under development by SickKids will contain differential time-released calcium and iron, to ameliorate the competition of iron and calcium for absorption, and have a smooth texture and appealing flavor. It should be noted that powders and other forms of supplements (e.g., chewable tablets) will be developed and tested for efficacy and consumer acceptability. Consumer research will be needed to determine the best form (size, color, coating), any problems with side effects and how that will affect compliance, and ways to increase compliance with the entire regimen of calcium.	Appeal with populations with steadily increasing wealth. Some nice business models (e.g., PowerBar) abound; however, these are expensive products that are likely never to reach US$1/day populations.
Price sensitivity	Purchasers are likely to go with the lowest-priced product. Lack of strong evidence also limits consumer interest. Market research is needed to determine what cost and quality of product women are willing to pay for.	Purchasers are likely to go with the lowest-priced product. Lack of strong evidence also limits consumer interest. Market research is needed to determine what cost and quality of product women are willing to pay for.	Suspect that there is significant price sensitivity that will require donor intervention to reduce costs in order to reach the most vulnerable populations.
Policy environment	World Health Organization (WHO) policy in areas where dietary calcium intake is low: calcium supplementation during pregnancy (at doses of 1.5 g to 2.0 g elemental calcium per day) is recommended for all women, but especially those at high risk of developing PE. However, few countries currently have a policy to give calcium in pregnancy and those that do, such as Bangladesh and Indonesia, only recommend 500 mg/day.	WHO policy in areas where dietary calcium intake is low: calcium supplementation during pregnancy (at doses of 1.5 g to 2.0 g elemental calcium per day) is recommended for all women, but especially those at high risk of developing PE. However, few countries currently have a policy to give calcium in pregnancy and those that do, such as Bangladesh and Indonesia, only recommend 500 mg/day.	WHO policy in areas where dietary calcium intake is low: calcium supplementation during pregnancy (at doses of 1.5 g to 2.0 g elemental calcium per day) is recommended for all women, but especially those at high risk of developing PE. However, few countries currently have a policy to give calcium in pregnancy and those that do, such as Bangladesh and Indonesia, only recommend 500 mg/day.

Demand Information	TECHNOLOGY/SOLUTION		
	Calcium tablets or powders	**Micronutrient powders for women (e.g., Sprinkles)**	**Heart bars**
Donors/ stakeholders	Multiple: United States Agency for International Development (USAID), WHO, United Nations Children's Fund, World Bank.	SickKids won a Saving Lives at Birth Grand Challenge in 2011. Saving Lives at Birth: A Grand Challenge for Development is an initiative jointly funded by Grand Challenges Canada, USAID, Norway's Foreign Ministry, the World Bank, and the Bill & Melinda Gates Foundation.[10]	Funding for the clinical trial was provided by the Bill & Melinda Gates Foundation and Fondo de Salud, CONACYT.[7,11]
Pre- and post-sales support	Providers need to advise mothers on the recommended dosage, emphasize adherence, and warn for side effects.	Providers need to advise mothers on the recommended dosage, emphasize adherence, and warn for side effects.	Providers need to advise mothers on the recommended dosage, emphasize adherence, and warn for side effects.
Need for demand creation	Plenty of opportunity exists for additional localized and ministry of health-level advocacy to increase demand. Demand strategies will need to focus on increasing information to women on why and how to take the entire regimen of calcium and how to manage any side effects that occur.	Plenty of opportunity exists for additional localized and ministry of health-level advocacy to increase demand. Demand strategies will need to focus on increasing information to women on why and how to take the entire regimen of calcium and how to manage any side effects that occur.	It will be challenging to create demand for what is anticipated to be a more expensive product.

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Biomarkers for Preeclampsia Screening

Preeclampsia (PE) diagnosis is based on symptoms, and it is made when the disease is already expressed. In contrast, PE screening is performed before any symptoms appear and aims to estimate the risk that the disorder will develop. While numerous maternal and fetal factors may predispose an individual woman to PE, screening by maternal history will detect only 30 percent of women who will develop PE,[1] and use of so-called risk factors has a low positive and negative predictive value for PE.[2,3] To date, no reliable test or symptom complex predicts the development of PE, and providers continue to rely on measuring blood pressure and proteinuria during focused antenatal care (ANC)4 to identify PE as early as possible (the onset of PE is usually after 20 weeks gestation). Unfortunately, although 80 percent of pregnant women received ANC at least once during the period between 2000 and 2010, only 53 percent received the World Health Organization (WHO) recommended minimum of four antenatal visits, thus limiting the ability to identify PE. In addition, most cases of eclampsia present in the third trimester of pregnancy, with approximately 80 percent of eclamptic seizures occurring intrapartum or within the first 48 hours following delivery. While the proportion of deliveries attended by skilled health personnel rose from 58 percent in 1990 to 68 percent in 2008, it has remained low in the WHO African Region and the WHO South-East Asia Region where only around 50 percent of deliveries were attended by skilled health personnel,[5] meaning a large percentage of women are not being cared for by a skilled birth attendant when they most need it.

A study on the effect of assessing risk factors on compliance with referral recommendations and found that of the various hypotheses tested, the geographic accessibility of the hospital and the pregnant woman's perception of her risk status were the two most important factors in determining the compliance rate.[6] If a biomarker[7] with reasonable specificity and sensitivity existed for PE and could be tested for as early as possible in the pregnancy, it would not only have the potential to substantially improve care—ensuring access to preventive strategies, closer prenatal and postpartum monitoring, recognition of PE earlier in the disease course, and timely access to the treatment package—but would also hopefully provide the additional benefit of assisting women in understanding their risk status. This in turn would improve attendance at ANC and postpartum care, compliance with instructions for care, and increase the likelihood of the presence of a skilled birth attendant at the time of birth. Authors of a WHO systematic review of screening tests for PE described the ideal test as being "simple, innocuous, rapid, inexpensive, reproducible, and noninvasive as well as easy to perform early in pregnancy to allow interventions to prevent when available or at least mitigate the development of the disease."[1] Identification of biomarkers for diagnosis of PE early in pregnancy is still largely in a stage of discovery.

PE is marked by exquisitely small changing levels of small molecule biomarkers and presently cannot be qualitatively predicted through a cheap, easy-to-use instrument such as a lateral flow diagnostic. In fact, testing based on any one angiogenic/anti-angiogenic factor has poor accuracy due to the "multi-factorial nature of the disease;" and it is more likely that an algorithmic assessment of multiple biomarker factors would be needed to make an accurate prediction.

"Major challenges in screening with the new markers are the relatively novel origin of the markers and the lack of gold standards to assess their concentrations. The field requires an independent standard center to provide marker calibration. Moreover, in countries where the clinics are widely distributed but testing is performed in a central laboratory, the issue of marker stability during transfer and storage becomes important."[1]

An ideal marker should be minimally invasive to obtain the sample, stable in the sample, be accurate and sensitive, and be able to be integrated within routine testing already used as a part of prenatal testing, and integrated into existing test platforms to reduce the need to purchase major new hardware.[1]

"Marker accuracy has not yet been set to evaluate the cost of surveillance since there is a need to decide on an acceptable detection rate and a false positive rate. Product cost is another unknown factor since the only products in the market today are Doppler sonography, placental protein 13 (PP13), placental growth factor (PIGF), and pregnancy-associated plasma protein A testing, and only the latter is included today in publically paid clinical services.[1]

The two tables below illustrate the various biomarkers currently being examined for prediction of preeclampsia.

Supply Information	TECHNOLOGY/SOLUTION					
	Chemical Biomarkers—TABLE 1					
	DELFIA® Xpress PlGF kit (product # 6007-0010)	**Elecsys PlGF/sFLT-1 and Elecsys PlGF**	**Congo Red Dot Test**	**Placental protein 13 maternal serum marker**	**VEGFR-1 preeclampsia marker**	**Predicting preeclampsia in normal and low-risk pregnancies: proteomics to profile urinary proteins**
Description	Quantitative determination of placental growth factor (PlGF) in maternal serum. In normal, uncomplicated pregnancy, free, unbound PlGF levels increase during the first and second trimester and then decline. The level of PlGF is typically decreased in maternal serum during both the first and the second trimesters of pregnancy in women who later develop preeclampsia (PE). This solid-phase, two-site fluoroimmunometric assay is based on the direct sandwich technique in which monoclonal antibodies and polyclonal antibodies are directed against the PlGF molecule. Limit of quantitation is typically 7 pg/mL.	Automated immunoassays specific for soluble fms-like tyrosine kinase 1 (sFlt-1) and PlGF.	Congo red dye may identify eclampsia if the disease is due to misfolded proteins that are Congophilic.[3]	PerkinElmer is developing convenient assays for detection of PlGF and the new serum maternal marker placental protein 13 (PP13) for early assessment of an elevated probability of development of PE during pregnancy.	Miraculins is investigating biomarkers (a VEGFR-1 polypeptide) that can predict the risk of PE.[5]	A workflow for evaluating the urinary proteomic profile of pregnant women to predict PE in normal and low-risk pregnancies has been developed and validated: six proteins were present only in urine samples from women with PE; an additional single protein was present in control samples and absent from preeclamptic samples.[6]
Characteristics applicable for low-resource settings	Currently validated, though needs to be made simpler, less costly.	Currently validated, though needs to be made simpler, less costly.	Highest potential for point-of-care screening test (meets ASSURED criteria).[8]	Sample source is blood serum. First tests on the markets will not be suitable for low-resource settings.	Sample source is blood serum. First tests on the markets will not be suitable for low-resource settings.	First tests on markets will not be suitable for low-resource settings.

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	DELFIA® Xpress PlGF kit (product # 6007-0010)	**Elecsys PlGF/sFLT-1 and Elecsys PlGF**	**Congo Red Dot Test**	**Placental protein 13 maternal serum marker**	**VEGFR-1 preeclampsia marker**	**Predicting preeclampsia in normal and low-risk pregnancies: proteomics to profile urinary proteins**
Developer and/or manufacturer	PerkinElmer, Inc.	Roche Diagnostics	Irina Buhimschi, Yale School of Medicine	PerkinElmer, Inc.	Isabella Caniggia, Samuel Lunenfeld, Research Institute of Mount Sinai Hospital, Toronto, Canada; Miraculins; Alere	Lucy Chappell, Kings College, London, UK
Status	The product was launched in October 2010. Commercialized in the European Union (EU). The DELFIA® Xpress PlGF kit has market approval in the EU, but not in Canada or the United States.	The technology has been commercialized in the EU and Canada. Has a CE mark.[9]	Clinical trials involving 347 women have been completed; more clinical studies are needed.[10,11]	The technology is in the clinical phase. Research kit available on AutoDELFIA and DELFIA platforms.	Preclinical phase.	Preclinical phase.
Efficacy/ effectiveness	Detection rate of 44% (when also tested with PP13) and false-positive threshold is set at 5%. When combined with five other biomarkers, the detection rate can be 99%.	The sFlt-1/PlGF ratio showed the best diagnostic power for both early-onset and late-onset preeclampsia. In addition, a cutoff value of 45 for the sFlt-1/PlGF ratio resulted in the best sensitivity and specificity for the diagnosis of all PE (97% and 95%, respectively), and for the diagnosis of early-onset PE (100% and 95%, respectively).[12,13]	Congo Red retention was more accurate at predicting indicated delivery for PE than protein-to-creatinine ratio (P<.001) and more accurate than the previously validated ratio of high-soluble fms-like tyrosine kinase 1 to placental growth factor (sFit1/PlGF) (P=.014).	Data not available.	Data not available.	Data not available.

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Manufacturing quality and capacity	PerkinElmer, Inc. is a large company, and a supplier of medical technologies. The current market is developed countries, thus capacity exists to accommodate other settings as well. This company can certainly arrange the financial resources necessary to increase supply if needed.	Roche is a large company, and a supplier of medical technologies. The current market is developed countries, thus capacity exists to accommodate other settings as well. This company can certainly arrange the financial resources necessary to increase supply if needed.	No, a technology transfer will be required.	PerkinElmer, Inc. is a large company, and a supplier of medical technologies. The current market is developed countries, thus capacity exists to accommodate other settings as well. Can certainly arrange the financial resources necessary to increase supply if needed.	No, a technology transfer will be required.	No, a technology transfer will be required.
Intellectual property ownership	Patent: Kit for diagnosis of preeclampsia United States Patent No. 8017734, issued September 13, 2011.	No data available.	No data available.	No data available.	Patent: Methods for Early Diagnosing of an Increased Risk of Preeclampsia United States Patent No. 20090104649, issued in July 2009.	No data available.

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Cost and cost drivers	Immunoassay that results in a colorimetric change that requires detection and quantification by a reader (ELISA). The specific hardware consumable of a microtiter plate coated by antibody is required.	Immunoassay that results in a colorimetric change that requires detection and quantification by a reader (ELISA). The specific hardware consumable of a microtiter plate coated by antibody is required.	The technology is too upstream for cost estimates.	The technology is too upstream for cost estimates.	The technology is too upstream for cost estimates.	The technology is too upstream for cost estimates.

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Delivery/ procurement channels	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a point-of-care [POC] test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine antenatal care (ANC).	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers, but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.
Sustainable business models	PerkinElmer, Inc. is a multinational company with reported revenue of approximately US$1.7 billion in 2010, serving customers in more than 150 countries.	Roche is the world's largest biotech company.	Not determined.	PerkinElmer, Inc. is a multinational company with reported revenue of approximately US$1.7 billion in 2010, serving customers in more than 150 countries.	Not determined.	Not determined.

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	Chemical Biomarkers—TABLE 1					
	DELFIA® Xpress PlGF kit (product # 6007-0010)	**Elecsys PlGF/sFLT-1 and Elecsys PlGF**	**Congo Red Dot Test**	**Placental protein 13 maternal serum marker**	**VEGFR-1 preeclampsia marker**	**Predicting preeclampsia in normal and low-risk pregnancies: proteomics to profile urinary proteins**
Existing demand	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.
Attractiveness	Requires high capital expenditure and a laboratory setting.	The test can be run in 18 minutes.	This is possibly a POC test.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.
Price sensitivity	No data available.	No data available.	No data available.	No data available.	No data available.	No data available.
Policy environment	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.
Donors/ stakeholders	None.	None.	McKern Award for Perinatal Research.[14]	None.	Unknown at this time.	Tommy's.
Pre- and post-sales support	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.
Need for demand creation	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.

Supply Information	TECHNOLOGY/SOLUTION					
	Chemical Biomarkers—TABLE 2					
	Proteomics in PE	**Screening and diagnosis in high risk pregnant women: a combination biomarker assay**	**Chronic hypertension in pregnancy: urine biomarkers for a predictive test**	**Epigenetic tool for PE prediction**	**Marinobufagenin as a PE indicator**	**Low-cost sensing strip for early detection**
Description	Over 500 plasma proteins have been identified and developed in a novel mass spectrometry method to simultaneously measure up to 30 proteins in a single sample. Researchers aim to measure the proteins in a much larger sample set to determine which combination of proteins will be the most sensitive predictive test for PE. Part of the Screening for Pregnancy Endpoints (SCOPE) Consortium (known as the MAPS study in the United Kingdom).[10]	Project to combine biomarkers simultaneously in a single blood assay to enhance their predictive capabilities and to provide a convenient tool for clinical use and allow fast and effective decision-making.[10]	Project to identify novel chemicals in the urine of women with hypertension which may be used to identify women likely to have problems in their pregnancy. Urinary biomarkers that will allow better discrimination between raised blood pressure and preeclampsia will also be investigated.[10]	Project to develop a database of epigenetic signatures, changes in DNA and proteins caused by nongenetic factors such as poor nutrition, smoking, and environmental contaminants that could be used as predictors of PE, and a cost-effective diagnostic tool to detect these markers in blood or urine.[15]	Study of initial evidence that elevated levels of the steroid hormone marinobufagenin (MBG) in urine are a very early indicator of PE in pregnant women. If true, this common and dangerous condition could be diagnosed early with a simple urine dipstick test and potentially prevented or treated with a molecule called resibufogenin, which counteracts MBG.[16]	Project to develop a low-cost sensing strip with a diagnostic reader to diagnose PE. The diagnosis is based upon the fact that there is an electrical current change when PE is present for the early detection and monitoring of this condition to avoid late-stage pregnancy complications.[16]
Characteristics applicable for low-resource settings	Academic R&D level.	Academic R&D level.	Academic R&D level.	Academic R&D level.	Academic R&D level.	Academic R&D level.
Developer and/or manufacturer	Richard Blankney, Manchester University, St. Mary's Hospital, Manchester, UK	Ian Crocker, St. Mary's Hospital, Manchester, UK	Dr. Kate Bramham, Dr. Lucy Chappell, Dr. Hiten Mistry, Pr. Lucilla Poston	Mahua Choudhury of University of Colorado, USA	Jules Puschett, TAMUS Health Science Center Research, USA	Zhenan Bao of Stanford University, USA
Status	Preclinical.	Preclinical.	Preclinical.	Preclinical.	Preclinical.	Preclinical.
Efficacy/ effectiveness	Not yet determined.	Not yet determined.	Not yet determined.	Not yet determined.	Not yet determined.	Not yet determined.
Manufacturing quality and capacity	Early-stage development—too soon to determine.	Early-stage development—too soon to determine.	Early-stage development—too soon to determine.	Early-stage development—too soon to determine.	Early-stage development—too soon to determine.	Early-stage development—too soon to determine.

Supply Information	TECHNOLOGY/SOLUTION					
	Chemical Biomarkers—TABLE 2					
	Proteomics in PE	**Screening and diagnosis in high risk pregnant women: a combination biomarker assay**	**Chronic hypertension in pregnancy: urine biomarkers for a predictive test**	**Epigenetic tool for PE prediction**	**Marinobufagenin as a PE indicator**	**Low-cost sensing strip for early detection**
Intellectual property ownership	Not determined.	Not determined.	Not determined.	Not determined.	Not determined.	Not determined.
Cost and cost drivers	Technology too upstream for cost estimates.	Technology too upstream for cost estimates.	Technology too upstream for cost estimates.	Technology too upstream for cost estimates.	Technology too upstream for cost estimates.	Technology too upstream for cost estimates.
Delivery/ procurement channels	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.	Depending on the level of technology and the type of personnel required, the technology may be at the referral, clinic, or community level (if it can be a POC test). Depending on the country, some countries have labs in health centers but most will not have labs in the most peripheral health care facilities. Ideally, biomarker screening happens at the first antenatal visit and is integrated into routine ANC.
Sustainable business models	Too early to determine.	Too early to determine.	Too early to determine.	Too early to determine.	Too early to determine.	Too early to determine.

Demand Information	TECHNOLOGY/SOLUTION					
	Chemical Biomarkers—TABLE 2					
	Proteomics in PE	**Screening and diagnosis in high risk pregnant women: a combination biomarker assay**	**Chronic hypertension in pregnancy: urine biomarkers for a predictive test**	**Epigenetic tool for PE prediction**	**Marinobufagenin as a PE indicator**	**Low-cost sensing strip for early detection**
Existing demand	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.	The market size is driven by the number of pregnant women.
Attractiveness	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.	Early stage technology, not yet optimized for low-resource settings.
Price sensitivity	Undetermined.	Undetermined.	Undetermined.	Undetermined.	Undetermined.	Undetermined.
Policy environment	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.	Low-resource setting referral systems are not yet set up to accommodate positive results from a predictive PE/E screening test.
Donors/ stakeholders	Tommy's	Tommy's	Tommy's	Gates Grand Challenge, Round 6—April 2011.	Gates Grand Challenge, Round 6—April 2011.	Gates Grand Challenge, Round 6—April 2011.
Pre- and post-sales support	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.	A POC test will require training but little support.
Need for demand creation	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.	There is a strong need to develop a system around this technology when sensitivity and specificity are sufficient to warrant clinical use.

Supply Information	TECHNOLOGY/SOLUTION
	Physical Biomarkers
	Doppler ultrasound
Description	The vascular dysfunction present in PE has been well documented. In normal pregnancies, the uterine vascular bed is a low-resistance circuit and blood flow continues throughout diastole. As resistance increases, diastolic velocity diminishes in relation to systolic flow. Vascular resistance can be estimated using arterial velocity waveforms obtained by Doppler ultrasonography. The procedure requires an ultrasound instrument capable of performing Doppler analyses—as an example, the MicroMaxx™ ultrasound system (SonoSite, Inc.), a third-generation hand-carried product. The MicroMaxx™ system weighs less than eight pounds, is the size of a laptop computer, and delivers image resolution and performance comparable to costly, conventional cart-based ultrasound systems weighing more than 200 pounds. SonoSite manufactures durable portable ultrasound devices designed to withstand military usage, including a 30-inch drop test, and to require no maintenance.
Characteristics applicable for low-resource settings	The moderate predictive power that can be achieved, and relatively high resources required, do not make uterine artery Doppler ultrasound measurements a strong standalone candidate as a biomarker to be measured in resource-limited settings. Typically, this would be part of a screening algorithm.
Developer and/or manufacturer	Multiple.
Status	Multiple commercialized.
Efficacy/ effectiveness	The currently available hemodynamic biomarkers—the uterine artery Doppler ultrasound measures—provide only moderate performance for detecting the pathology underlying PE, and would be challenging to implement, due to the high level of resources required.
Manufacturing quality and capacity	Multiple in production capable of meeting anticipated demand.
Intellectual property (IP) ownership	Highly competitive IP landscape.
Cost and cost drivers	Instrument cost (US$20,000–US$60,000) is driven by IP and by the sensitive probe components.
Delivery/ procurement channels	Data not available.
Sustainable business models	Data not available.

Demand Information	TECHNOLOGY/SOLUTION
	Physical Biomarkers
	Doppler ultrasound
Existing demand	Data not available.
Attractiveness	Data not available.
Price sensitivity	Data not available.
Policy environment	None.
Donors/ stakeholders	Imaging the World, etc.
Pre- and post-sales support	Requires extensive training.
Need for demand creation	Data not available.

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[2] PerkinElmer. Pre-eclampsia countdown newsletter. Waltham, MA: PerkinElmer, Inc.; 2009. Available at: http://www.perkinelmer.de/Content/RelatedMaterials/NLT_PlGFCountdownNews032010.pdf. Accessed January 12, 2012.

[3] Congo Red Dot Test for preeclampsia page. Maternal and Neonatal Directed Assessment of Technology (MANDATE) website. Available at: http://www.mnhtech.org/technology/technologies-in-development/congo-red-dot-test/. Accessed January 31, 2012.

[4] NOTE: Focused ANC is evidence-based, goal-directed care that is tailored to the gestational age of pregnancy and individualized to each woman. It emphasizes quality of visits over quantity of visits and is conducted by a skilled health care provider. Goals of focused ANC include early detection and treatment of complications, prevention of problems, birth preparedness/complication readiness, and the promotion of healthy practices to help ensure a positive health outcome for the woman and her baby. Focused ANC is provided through a women-centered approach that values the dignity and value of each woman and her family.

[5] Miraculins preeclampsia markers page. MANDATE website. http://mnhtech.org/technology/technologies-in-development/miraculins-pre-eclampsia-markers/. Accessed January 31, 2012.

[6] Preeclampsia page. Tommy's website. Available at: www.tommys.org/Page.aspx?pid=358. Accessed January 31, 2012.

[7] NOTE: The official National Institutes of Health definition of a biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

[8] NOTE: The World Health Organization Sexually Transmitted Diseases Diagnostics Initiative (SDI) has developed the ASSURED criteria as a benchmark to decide if tests address disease control needs: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users.

[9] Roche Diagnostics announces CE launch of first diagnostic Preeclampsia Test [press release] Rotkreuz, Switzerland: Roche Diagnostics; January 6, 2009.

[10] Huynh N. Congo red dot test: a groundbreaking method to diagnose preeclampsia. *Yale Scientific Magazine*. 2003. Available at: http://www.yalescientific.org/2010/12/congo-red-dot-test-a-groundbreaking-method-to-diagnose-preeclampsia/. Accessed January 31, 2012.

[11] Mateus J, Lu F, Bytautiene E, et al. Effect of continuous infusion of vascular endothelial growth factor on blood pressure in a mouse model of preeclampsia induced by SFLT-1 overexpression. *American Journal of Obstetrics and Gynecology*. 2009;201(6 suppl):S12–S13.

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[15] Epigenetic Diagnostic Tool page. MANDATE website. Available at: http://mnhtech.org/technology/technologies-in-development/epigenetic-diagnostic-tool/. Accessed January 31, 2012.

[16] Grants awarded page. Grand Challenges in Global Health website. Available at: http://www.grandchallenges.org/Explorations/Pages/GrantsAwarded.aspx?Topic=Create%20New%20Technologies%20to%20Improve%20the%20Health%20of%20Mothers%20and%20Newborns%20&Round=6&Phase=all. Accessed January 31, 2012.

Blood Pressure Measurement

Hypertension in pregnancy is defined as a diastolic blood pressure (BP) reading >90 mm Hg or a systolic blood pressure reading >140 mm Hg on two consecutive readings four hours apart. It is generally accepted that the onset of a new episode of hypertension during pregnancy (with persistent diastolic BP >90 mm Hg) with the occurrence of substantial proteinuria can be used as criteria for identifying preeclampsia.[1] Unfortunately, in low-resource settings the detection of hypertension is often missed because suitable, accurate, and reliable BP measurement devices are not available. If equipment is available in these settings, there is too often a lack of training in the skills and methods necessary to get a reliable measurement.[2]

World Health Organization (WHO) experts have determined that although the ausculatory[3] technique has remained essentially unchanged for over a century, this technique can be inaccurate due to a faulty application of the method and poor distinction of the different Korotkoff sound phases. In particular, the estimation of diastolic blood pressure using the auscultatory technique is limited in accuracy[2] and subject to observer error such as digit preference and observer bias.[4,5] Furthermore, concerns about the toxicity of mercury for the users and the environment have added to the body of evidence that traditional devices are inappropriate for low-resource settings. Some countries have banned the use of mercury devices. There is a need for accurate and affordable BP measurement technologies.

There are several barriers to accurate and affordable blood pressure measurement, particularly in developing countries. These include:

- The absence of accurate, easily-obtainable, inexpensive devices for BP measurement.
- The frequent marketing of non-validated BP measuring devices.
- The relatively high cost of BP devices given the limited resources available.
- Limited awareness of the problems associated with conventional BP measurement techniques.
- A general lack of trained manpower and limited training of personnel.

The dabl® Educational Trust, Ltd. nonprofit sponsored by industry[6] maintains an up-to-date accuracy analysis of currently available BP measurement devices. To fulfill the requirements related to BP measurement in low-resource settings, a BP measuring device should be affordable, easy to calibrate, and extremely simple to use but at the same time be accurate and robust so that it can be easily used for repeated BP measurements.[2] In 2002 WHO established a committee to develop technical specifications for an accurate and affordable BP measuring device for clinical use in low-resource countries.[7] The objectives of the project were to elaborate on the preferred characteristics and to develop

technical specifications for such a device. A challenge was issued by WHO to industry stipulating that devices fulfilling the specifications must then be subjected to independent validation according to the International Protocol of the European Society of Hypertension,[8] and having fulfilled this requirement the device had then to undergo testing in field conditions according to a predetermined protocol in clinical and environmental circumstances that would reflect the ultimate circumstances of use.

Out of several devices[9] tested, only one device—the Omron HEM-Solar—fulfilled the validation criteria of the International Protocol8 for systolic blood pressure and also performed well in field testing carried out on 716 subjects in three centers in Uganda and Zambia where health care workers preferred it to the mercury sphygmomanometer.[10] Since a number of studies have demonstrated that oscillometric monitors may produce inaccurate measures in patients with heart and circulation problems (including preeclampsia), it is important to note that the Omron HEM-Solar has not yet been tested with pregnant women.

Furthermore, the WHO specification for low-cost BP devices has forced oscillometric device manufacturers to choose lower-quality sensors that are more subject to drift and errors associated with mishandling. Thus, the importance of frequent calibration cannot be underestimated. That said, adherence to a calibration schedule and any equipment maintenance is a general shortcoming in most low-resource settings, thus there is a tradeoff between cost of the device and accuracy when normal calibrations cannot be guaranteed. In conjunction with advancing novel BP measurement technologies, there is a need to solve the calibration challenge by developing calibration technologies and devices that need less frequent calibration or none at all and by developing calibration standards and processes that are low cost and require minimal skills to implement. Duke University is working on a simple calibration tool design that leverages basic manometer principles and a column of water that can be fabricated on site from local materials.

To impact morbidity and mortality from preeclampsia/eclampsia, access to BP measurement should be extended to the community level, thus greatly improving identification of women with hypertension and, by consequence, increasing the chance that she will have access to the treatment package[1] and increasing the likelihood that she and her baby will survive.

The two tables below scrutinize promising BP measurement devices and methods.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1		
	Generic ausculatory mercury blood pressure measurement kits with stethoscope	**Generic ausculatory (aneroid and digital) blood pressure measurement kits with stethoscope such as the Prestige**	**Accoson Greenlight 300**
Description	These devices are used to measure BP according to the original ausculatory technique described by Riva Rocci and Korotkoff over a century ago. The measuring observer must be trained to use a stethoscope to auscultate the Korotkoff sounds over the brachial artery. This technique is usually referred to as conventional blood pressure measurement.	Use same ausculatory principle as traditional mercury BP measurement devices. Both aneroid and digital have the advantage of obviating use of toxic mercury though aneroid is more susceptible to terminal digit bias. Both aneroid and digital require frequent calibration and are subject to inaccurate readings when exposed to harsh handling.	Manual, self-calibrating, Hg-free, ausculatory device.
Characteristics applicable for low-resource settings	Gold standard with regards to accuracy in general population and pregnant women. No external power requirements,	No toxic mercury. Digital blood pressure measurement kits require batteries.	Self-calibration obviates need for gold standard and appropriate skill set for six-month calibration cycle and ensures accuracy. No toxic mercury; needs batteries.
Developer and/or manufacturer	Multiple.	Multiple.	Accoson; developed in a joint project by AC Cossor & Son, the Regional Medical Physics Department of the Freeman Hospital, and the University of Newcastle.
Status	Multiple commercialized and validated.	Multiple commercialized and validated to British Hypertension Society (BHS) protocol.	Commercialized and validated to BHS protocol. US Food and Drug Administration approved. Compliant with the European standards EN1060-1, EN1060-2 and EN1060-3. First non-automated mercury-free device for ausculatory BP measurement to pass the International Protocol for validation of BP measuring devices in adults.[11]
Efficacy/ effectiveness	Only one model of the many mercury sphygmomanometers available, the PyMah (Pymah Corporation, Flemington, NJ), has been validated according to both protocols and is recommended. Because mercury sphygmomanometers generally adhere to a basic design with standard components, it is probably reasonable to assume that most, if not all, mercury sphygmomanometers would be of similar accuracy.	The standard aneroid sphygmomanometer has only been formally validated according to the calibration procedure of the BHS protocol, and the results support reservations about aneroid devices because of their susceptibility to becoming inaccurate with use without this being apparent to the user.	The Greenlight 300 has been validated to the International Protocol by Graves, et al.[11] Not evaluated yet for use in detecting hypertension in pregnant women. No evidence of use or acceptability for low-resource settings though the self-calibration feature is very strong and is unique to this device.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1		
	Generic ausculatory mercury blood pressure measurement kits with stethoscope	**Generic ausculatory (aneroid and digital) blood pressure measurement kits with stethoscope such as the Prestige**	**Accoson Greenlight 300**
Manufacturing quality and capacity	Multiple manufacturers of this technology.	Multiple manufacturers of this technology.	Manufactured in the UK; likely high ability to meet potential demand as the manufacturer exports products to more than 70 countries.
Intellectual property (IP) ownership	Mature technology, no IP barriers.	Mature technology, very low IP barriers.	Very likely the self-calibrating feature is covered by IP.
Cost and cost drivers	US$30 The market is highly competitive with sourcing of production to low-cost regions such as Asia-Pacific.[1]	~US$10; branded devices ~US$25.	US$230
Delivery/ procurement channels	Could be used at the community level.	Could be used at the community level.	Three US distribution offices and one international distribution office in the United Kingdom. No indications of low-resource setting distribution. Could be used at the community level.
Sustainable business models	Presence of multiple manufacturers is evidence that this market is sustainable.	Presence of multiple manufacturers is evidence that this market is sustainable.	The company is a registered, quality-assured firm under ISO9001:2000.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1		
	Generic ausculatory mercury blood pressure measurement kits with stethoscope	**Generic ausculatory (aneroid and digital) blood pressure measurement kits with stethoscope such as the Prestige**	**Accoson Greenlight 300**
Existing demand	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate)[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate)[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate).[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]
Attractiveness	Gold standard but requires extensive training.	Low cost but requires frequent calibration.	Self-calibration feature is a very strong feature that is unique to this device.
Price sensitivity	Mercury is an expensive commodity and the market is decreasing. Expect both supply and demand to drop off substantially over the next decade. Customers will be less interested over time.	In general, hospital market is used to paying quite a bit for these as sophisticated medical devices in developed countries while developing countries are discovering the big box store, Chinese-made versions that are typically not robust and do not offer any indication to the user that accuracy is inadequate. Need user training to identify calibration and quality concerns in order to increase willingness to pay for quality.	Willingness to pay for zero calibration has not been determined. Need a cost-effectiveness study that looks at both improvement in clinical outcomes and the cost savings associated with obviating need for the calibration process. Negotiated prices for large-scale public health purchases have not been determined
Policy environment	Mercury sphygmomanometers are typically the gold standard for the European Society of Hypertension International Protocol (ESH-IP) protocols. Alternative approaches such as intra-arterial blood measurement are not practical.	In 2010, a revised version of the ESH-IP with more stringent criteria was published.	In 2010, a revised version of the ESH-IP with more stringent criteria was published.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1		
	Generic ausculatory mercury blood pressure measurement kits with stethoscope	**Generic ausculatory (aneroid and digital) blood pressure measurement kits with stethoscope such as the Prestige**	**Accoson Greenlight 300**
Donors/ stakeholders	None.	None.	Mayo Clinic, Rochester, and the Mayo Foundation.
Pre- and post-sales support	Requires the most training.	Requires frequent calibration.	Does not require calibration.
Need for demand creation	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2		
	Automated and semi-automated oscillometric devices (Omron HEM-Solar [M1 Plus])	**Tensoval duo-control device**	**Center for Bioengineering Innovation & Design hypertension detection device**[12]
Description	Automated and semi-automated (requiring hand pumping to pressurize cuff) devices remove sources of error such as observer bias and terminal digit preference and thereby improve the overall accuracy. Oscillometric devices do not use the auscultation of Korotkoff sounds but instead detect oscillations in the occluded artery as the cuff is deflated and calculate BP using algorithms. The Omron HEM-Solar is a semiautomatic solar-powered BP monitor and the only one of its class to receive a recommendation from the dabl® Educational Trust. Oscillometric devices are becoming more accurate, and the revised ESH-IP, by acknowledging this trend, will allow more accurate devices to enter the market. The indirect nature of oscillatory BP measurement poses particulary problems for ensuring accuracy. Critical assessment has done much to improve standards, but a solid theoretical understanding of the technique has not been formulated, and further work is required.	Noninvasive BP measurement is typically dependent on either auscultation or oscillometry. The Tensoval duo-control device uses auscultatory and oscillometric technology to determine BP.	Handcrank power source; no readout—simply yes/no result for hypertension; designed for low cost <US$10; oscillometric.
Characteristics applicable for low-resource settings	Eliminates observer bias and terminal digit rounding. The device can run on batteries as well as solar power.	Uses two modes to improve accuracy in subset populations such as pregnant women. Needs batteries.	<US$10; ease of use (no interpretation required). No external power requirements.
Developer and/or manufacturer	Omron.	Hartmann-Rico www.hartmann.de www.tensoval.com	Jhpiego, Center for Bioengineering Innovation & Design (CBID)
Status	Commercialized and validated to BHS protocol.	Commercialized and validated to BHS with a grade A recommendation.[14] Clinical study underway in rural Africa (Ethiopia, Tanzania, and Zambia) under the CRADLE (formerly COBRA) project.[15]	Field testing in rural communities has been planned in Nepal; not commercialized; not validated.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2		
	Automated and semi-automated oscillometric devices (Omron HEM-Solar [M1 Plus])	**Tensoval duo-control device**	**Center for Bioengineering Innovation & Design hypertension detection device**[12]
Efficacy/ effectiveness	The Omron HEM-Solar is the only BP measurement device that meets WHO specifications and has been validated according to the International Protocol of the European Society of Hypertension. While this device passed laboratory testing, field tests in Uganda and Zambia demonstrated the device fulfilled criteria for systolic BP but not diastolic BP. The device has not been evaluated yet for use in detecting hypertension in pregnant women.	Validated to the BHS standard. Not evaluated yet for use in detecting hypertension in pregnant women.	Not yet determined per established international protocols. Not evaluated yet for use in detecting hypertension in pregnant women.
Manufacturing quality and capacity	Manufactured in Japan. Likely high ability to meet potential demand as the manufacturer is a large international supplier of BP measurement technology.	Manufactured in Germany. Likely high ability to meet potential demand as the manufacturer is a large international supplier of medical products.	Developer is investigating Chinese manufacturing due to low costs.
Intellectual property ownership	A live teardown indicates that there is no patentable hardware to the technology though the algorithms are coded and are therefore proprietary.[16]	Proprietary technology.	Needs to be evaluated.
Cost and cost drivers	~US$32 to US$130	~US$75[17]	A sub US$10 device seems aspirational. Jhpiego states that cost of goods is currently at US$15 per unit,[12] however this has not been confirmed. There are similar devices on the market for ~US$30. At this low end, it may be very difficult to sell at <US$20 unless economies of scale reach >1M units per year. Hand-crank charging may not be cost effective using Powerfree Education and Technology (PET) and Freeplay Energy technologies as a baseline for the added cost of hand-crank power. There is considerable extra cost for the crank parts and storage capacitor.
Delivery/ procurement channels	Could be used at the community level.	Product launched in Europe in drugstores in 2007. In 2008, Tensoval captured 20 percent of the BP measuring devices in the European pharmacy market. Product launched in China in July 2010.[18] Could be used at the community level.	Not yet commercialized. Could be used at the community level.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2		
	Automated and semi-automated oscillometric devices (Omron HEM-Solar [M1 Plus])	**Tensoval duo-control device**	**Center for Bioengineering Innovation & Design hypertension detection device**[12]
Sustainable business models	Surprisingly, manufacturers have been slow to produce automated sphygmomanometers for clinical use in hospitals to satisfy the large market that has arisen from the banning of mercury in some countries and the recommendation not to replace mercury sphygmomanometers in others, such as the United Kingdom and Ireland. There is evidence that the manufacturing industry is now aware of the need for accurate automated devices to replace mercury sphygmomanometers.[19]	This is a new class of BP measurement devices targeted at niche markets/specific populations with pathologies that lead to common BP measurement error.	Product still in development phase.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2		
	Automated and semi-automated oscillometric devices (Omron HEM-Solar [M1 Plus])	**Tensoval duo-control device**	**Center for Bioengineering Innovation & Design hypertension detection device**[12]
Existing demand	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate).[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate).[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]	The application of this technology is broader than just screening or diagnosis for hypertension in pregnant women. Therefore the market size is driven by the number of health facilities, providers, and communities. Jhpiego estimates that the BP measurement market is 10 million units (unsubstantiated estimate).[12] A market research report forecasts that the BP measurement market will be US$2.2 billion by 2015, driven largely by "an expanding proportion of old age people suffering from BP problems, technological advancements in monitors, growing consumer awareness about benefits of regular measurements and monitoring, intensifying direct-to-consumer advertising and growing stress on health care in developing countries."[13]

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2		
	Automated and semi-automated oscillometric devices (Omron HEM-Solar [M1 Plus])	**Tensoval duo-control device**	**Center for Bioengineering Innovation & Design hypertension detection device**[12]
Attractiveness	According to WHO-sponsored researchers: "There was no need to assess competence because unlike auscultatory measurement the device is simple to use and no testing of individual competence is required." It performed well in field testing carried on 716 subjects in three centers in Uganda and Zambia where health care workers preferred it to the mercury sphygmomanometer.[10] Some 85 percent of health care professionals rated the solar device as good or very good, with 97 percent recommending its use.	Uses two modes to improve accuracy.	It will be very difficult for this product to meet the WHO specifications for appropriate technologies for low-resource settings and for it to pass BHS protocol as there is no BP readout. This limits its utility and market as BP trending is an important metric to rule out whitecoat hypertension etc.
Price sensitivity	In general, the hospital market is use to paying quite a bit for these as sophisticated medical devices in developed countries while developing countries are discovering the big box store, Chinese-made versions that are typically not robust and do not offer any indication to the user that accuracy is inadequate. Need user training to identify calibration and quality concerns in order to increase willingness to pay for quality.	Niche market will prevent scaling required to decrease prices to be competitive. Customers willing to pay quite a bit to get the performance.	Seems the limited performance (non-numeric readout) will limit the market to lowest-resource niche. Decreased willingness to pay.
Policy environment	In 2010, a revised version of the ESH-IP with more stringent criteria was published.	Nothing specific to note.	In 2010, a revised version of the ESH-IP with more stringent criteria was published.
Donors/ stakeholders	Validation study supported by the WHO Committee on Blood Pressure Measurement in Low-Resource Settings.	Clinical study funded by Tommy's—a charity registered in England that funds research.[15] Research partners include: Women's Academic Health Centre, King's Health Partners, King's College London.	Jhpiego developed this technology under a five-year project called Accelovate which is funded by the United States Agency for International Development.[20]
Pre- and post-sales support	Requires calibration. Requires 15 minutes of training.	Requires calibration.	Requires calibration.
Need for demand creation	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.	Cost and how easy the device is to calibrate are important factors if the device is intended for care at the community level. However, at this point, there is a trade-off between cost and how easy the device is to calibrate.

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Proteinuria Measurement

Proteinuria is defined as more than 300 mg of protein in the urine per 24 hours, and its presence along with hypertension, confirms diagnosis of preeclampsia in a pregnant woman. Positive maternal and perinatal outcomes for women with preeclampsia/eclampsia (PE/E) depend on how soon the condition is identified and how quickly the woman has access to the treatment package.[1] Secondary prevention for PE/E has focused on antenatal screening for high blood pressure and proteinuria as part of focused antenatal care (ANC).[2] The presence of proteinuria changes the diagnosis from gestational hypertension to PE, and detection of proteinuria is vital for making a diagnosis of PE. There are currently several ways to measure protein in the urine, but these vary in accuracy, cost, simplicity, and feasibility. Measurement of protein in a 24-hour urine collection is considered the gold standard and more recently 12-hour collections (and even 2-hour collections) have been validated, but such collections are not always feasible and may be impractical in low-resource settings. Although the use of dipsticks to analyze random urine samples is relatively simple, several challenges hinder their effectiveness including poor correlation with protein analysis in 24-hour urines, inaccuracy due to the hour-to-hour variability of protein excretion, inaccuracy if the urine is dilute, dependency on observer interpretation, a possible false positive if the pregnant woman has a urinary tract infection or the urine is contaminated with blood or vaginal secretions, and the susceptibility of dipsticks to deterioration from humidity and temperature. Problems with dipstick analysis can be avoided by measuring the urine's protein-to-creatinine ratio, but this may be impractical if urgent assessment is needed and cannot be used for monitoring or quantifying proteinuria in pregnancy. There are urinalysis devices that are promising, such as a cartridge-based automated analyzer and creatinine/protein dipsticks, but these require additional testing and/or adaptation to make them more accurate, simple, or affordable.

In low-resource settings, protein dipsticks are often used at the point of care. This is because implementing the gold standard of protein measurement (urine collection over 24 hours and analysis using a manual or automated methods) is not practical in such a setting. Common dipsticks typically detect albumin through a reaction with a blue dye. However, their correlation with 24-hour test results can vary. More advanced dipsticks measure the ratio of protein to creatinine which can correlate more closely to 24-hour tests. Dipsticks can be assessed against a standard color or fed into an automated reader. Automated readers help standardize dipstick results.

The table below examines several options for proteinuria measurement—both technologies commonly used and in development.

Supply Information	TECHNOLOGY/SOLUTION				
	UNICEF Supply Catalogue urine dipstick	**Bayer Multistix Pro 10LS**	**Bayer Clinitek 50**	**Bayer DCA 2000 (now called DCA Vantage)**	**Center for Bioengineering Innovation and Design (CBID) proteinuria pen**
Description	Medi-Test Combi 2 test strips detect the presence of glucose and protein (albumin) in urine. Results in 60 seconds.	Creatinine/protein dipstick; firm plastic strips with several separate reagent areas; results in 60 seconds. The strips may be read visually, requiring no additional laboratory equipment for testing. However, dipstick results agree better with the quantitative assays if read by a reflectometer.[3] Can be read instrumentally, using the Bayer Clinitek® family of urine chemistry analyzers and the appropriate program module/card. An example is the Bayer Clinitek 50 Urine Chemistry Analyzer.	Quantitative dipstick reader. Lightweight, portable. Does not correct for creatinine thus better suited to 12- or 24-hour assessment (not spot). Less than a minute. No interpretation of results required. Multiple markets across all urinalysis including: leukocytes, ketone, pH, blood, glucose, specific gravity, protein, bilirubin, nitrite, and urobilinogen.	Cartridge-based automated albumin/creatinine ratio (ACR) analyzer that provides an immediate result (7 minutes) of the ACR on spot urine. Load cartridge with sample and insert into the analyzer. Device stores up to 4000 records; easily downloaded and transferred to a PC. Print results. Color touch-screen display. Corrects for creatinine.	A pregnant woman's urine is exposed to a mark on paper made by a felt-tip or ballpoint pen filled with testing solution, which is then exposed to a pregnant woman's urine. If the mark turns the color of the pen's cap, the test is positive. Gives albumin but not creatinine. Takes less than a minute.
Characteristics applicable for low-resource settings	Point of use. No power supply needed.	Point of use. No power supply needed.	Optional battery pack allows 200 dipstick reads per charge—obviating need for reliable power.	Power supply needed; ACR can be performed on spot urine by an automated analyzer.	Point of use. No power supply needed.
Developer and/or manufacturer	Macherey-Nagel GmbH	Bayer/Siemens	Bayer/Siemens	Bayer/Siemens	CBID and Jhpiego at the Johns Hopkins University.
Status	Commercialized.	Commercialized.	Commercialized.	Commercialized.	Preclinical; Jhpiego and CBID will continue to refine the design and engineering and then conduct a pilot study in rural southern Nepal to assess the test's acceptability and feasibility for use at the community and household levels by community health workers and pregnant women.

Supply Information	TECHNOLOGY/SOLUTION				
	UNICEF Supply Catalogue urine dipstick	**Bayer Multistix Pro 10LS**	**Bayer Clinitek 50**	**Bayer DCA 2000 (now called DCA Vantage)**	**Center for Bioengineering Innovation and Design (CBID) proteinuria pen**
Efficacy/ effectiveness	Poor correlation with protein analysis in 24-hour urines; inaccuracy due to the hour-to-hour variability of protein excretion; inaccuracy if the urine is dilute; dependency on observer interpretation; a possible false positive if the pregnant woman has a urinary tract infection or the urine is contaminated with blood or vaginal secretions.	Protein/creatinine dipsticks have limited utility as a screening tool in pregnant women. While nonpregnant cohorts show sensitivity and specificity of 53.7% and 97.6%, respectively, the device does not work as well for pregnant cohorts (sensitivity: 19%–59%; specificity: 45.4%–84.2%).[4]	As a quantitative tool, enables trend tracking. No studies correlate this device directly to PE/E outcomes, and systematic reviews have called into question the correlation of proteinuria quantification to clinical outcomes. As a spot reader, a very questionable correlation to clinical outcomes and not a substantial improvement over dipsticks to warrant $500. As a total protein reader over 12/24 hours, clinical correlation is weak but is better than a spot dipstick.	Much better as a spot reader than non-creatinine correction tests, though correlation of albumin-only protein readers to overall maternal outcomes is quite weak. The ACR (DCA 2000) is strongly predictive for the presence or absence of significant proteinuria, with positive likelihood ratio of 27.4 and negative likelihood rates of 0.0.[5] The device tested was highly accurate, allowing the authors to set a threshold that detected significant proteinuria with a sensitivity of 94% and a specificity of 94%.[5] It has been hypothesized that microalbuminuria may facilitate diagnosis of preeclampsia earlier in its clinical course, as it may accurately reflect glomerular dysfunction. However, currently the evidence for this is inconclusive.[6]	Pilot study in Nepal; results are not yet available.

Supply Information	TECHNOLOGY/SOLUTION				
	UNICEF Supply Catalogue urine dipstick	Bayer Multistix Pro 10LS	Bayer Clinitek 50	Bayer DCA 2000 (now called DCA Vantage)	Center for Bioengineering Innovation and Design (CBID) proteinuria pen
Manufacturing	There are a series of Medi-Test paper strip tests for multiple diagnoses, and they distribute worldwide.	We do not see significant increased demand for this type of test until both sensitivity and specificity in detecting proteinuria in pregnant women increases.	Large market, multiple analytes. This technology is representative of several that do similar urinalysis function. Competition exists though Bayer is a substantial player in this market. Suspect changes in demand will not overcome manufacturing capacity or ability to predict and adjust capacity.	Large market, multiple analytes. This technology is representative of several that do similar urinalysis function. Competition exists though Bayer is a substantial player in this market. Suspect changes in demand will not overcome manufacturing capacity or ability to predict and adjust capacity.	Manufacturing strategy not yet developed.
Intellectual property ownership	Unclear; distributed by UNICEF but perhaps Macherey-Nagel GmbH still retains IP for private-sector distribution.	Priority technology by Siemens/Bayer. However, it is likely all relevant patents are expired since this technology has been on the market since 1978 or earlier.[7]	This is a simple dipstick reader—many similar products with some variation in the actual reagents and strip tests IP (likely patents and manufacturing know-how). As a mature technology, patents are likely expired.	Priority technology by Siemens/Bayer.	Data not available.
Cost and cost drivers	US$3.28 for a pack of 100 or ~US$.04 per test for.[8]	One bottle of 100 strips for US$349.95 or US$3.50 per test.[9]	Lowest cost of quantitative readers at US$500.	The analyzer costs US$2,500 to US$5000. The microalbumin/ creatinine regent kits cost US$100 for ten (US$10 each).	Designed to be cheaper than current strip tests. Developers assert that the price will be ~US$1.00/pen (400 tests).
Delivery/ procurement channels	Community.	Community.	Clinic.	Point-of-care test; therefore can be used in antenatal clinics.	Community.
Sustainable business models	These products have been on the market for a long time. Less risk here until a better product comes up.	Multinational corporation with this product on the market for a long time. Less risk here until a better product comes up.	This could be positioned as a more portable lab-independent technology based on the battery power flexibility.	This test was originally developed for women with diabetes to screen for micro-albuminuria as an early indicator of renal disease but has been assessed specifically for pregnancy hypertension.	Unknown, as the exact niche of this product is unclear.

Demand Information	TECHNOLOGY/SOLUTION				
	UNICEF urine dipstick (Medi-Test Combi 2)	Bayer Multistix Pro 10LS	Bayer Clinitek 50	Bayer DCA2000 (now called DCA Vantage)	Center for Bioengineering Innovation and Design (CBID) proteinuria pen
Existing demand	Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive a dipstick test at the first ANC visit, at 20 weeks, if blood pressure is elevated, when they arrive in labor, and at postpartum visits (2 days and 7 days postpartum). Once PE is diagnosed, a woman will be tested many times.	Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive a dipstick test at the first ANC visit, at 20 weeks, if blood pressure is elevated, when they arrive in labor, and at postpartum visits (2 days and 7 days postpartum). Once PE is diagnosed, a woman will be tested many times.	Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive a dipstick test at the first ANC visit, at 20 weeks, if blood pressure is elevated, when they arrive in labor, and at postpartum visits (2 days and 7 days postpartum). Once PE is diagnosed, a woman will be tested many times.	Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive a dipstick test at the first ANC visit, at 20 weeks, if blood pressure is elevated, when they arrive in labor, and at postpartum visits (2 days and 7 days postpartum). Once PE is diagnosed, a woman will be tested many times.	Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive a dipstick test at the first ANC visit, at 20 weeks, if blood pressure is elevated, when they arrive in labor, and at postpartum visits (2 days and 7 days postpartum). Once PE is diagnosed, a woman will be tested many times.
Attractiveness	Can be read visually. Result in 1 minute.	Can be read visually. Result in 1 minute.	Quantitative result—no interpretation of results required. Result in 1 minute.	Quantitative result—no interpretation of results required. Results in 7 minutes.	This test is designed to be easy for both semiliterate health care workers and pregnant women. Result in less than a minute.
Price sensitivity	Customers in low-resource settings buy these because they are the lowest cost and they are willing (knowingly or not) to sacrifice accuracy.	Slight increase in accuracy (seen in clinical results) for these tests does not seem to justify the added costs.	Difficult to estimate until there is a clear determination of accuracy.	Too costly and complex for low-resource settings, public health centers, and community use.	Too costly and complex for low-resource settings, public health centers, and community use.
Policy environment	No policy barriers, though there is little motivation to champion and advocate for such a low-performing test.	No policy barriers, though there is little motivation to champion and advocate for such a low-performing test.	No policy barriers, though there is little motivation to champion and advocate for tests with <80% sensitivity/specificity.	No policy barriers. There are practical barriers to 24-hour collection at public health centers and the community level.	No policy barriers. There are practical barriers to 24-hour collection at public health centers and the community level.

Demand Information	TECHNOLOGY/SOLUTION				
	UNICEF urine dipstick (Medi-Test Combi 2)	**Bayer Multistix Pro 10LS**	**Bayer Clinitek 50**	**Bayer DCA2000 (now called DCA Vantage)**	**Center for Bioengineering Innovation and Design (CBID) proteinuria pen**
Donors/ stakeholders	UNICEF is presumably a stakeholder.	None known at this time.	None known at this time.	None known at this time.	CBID and Jhpiego received $100,000 from USAID, and have collected ~$50,000 in additional funds through business plan competitions and grants. They received accolades from the Lemelson Foundation, the Duke Global Health Institute, and ABC News.
Pre- and post-sales support	Dipstick tests are easy to use and require little training. However, visually read dipsticks are open to misinterpretation.	Dipstick tests are easy to use and require little training. However, visually read dipsticks are open to misinterpretation.	Require no interpretation. Training required is minimal.	Require no interpretation. Training required is minimal.	Dipstick tests are easy to use and require little training. However, visually read dipsticks are open to misinterpretation.
Need for demand creation	Not recommended.	Not recommended.	Too soon to tell.	Only at levels higher than the primary health center.	Only at levels higher than the primary health center.

References

[1] NOTE: The treatment package includes inpatient monitoring, anticonvulsive and antihypertensive therapy, optimal timing of childbirth, and skilled attendance at birth.

[2] NOTE: Focused ANC is evidence-based, goal-directed care that is tailored to the gestational age of pregnancy and individualized to each woman. It emphasizes quality of visits over quantity of visits and is conducted by a skilled health care provider. Goals of focused ANC include early detection and treatment of complications, prevention of problems, birth preparedness/complication readiness, and the promotion of healthy practices to help ensure a positive health outcome for the woman and her baby. Focused ANC is provided through a women-centered approach that values the dignity and value of each woman and her family.

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Risk Management Tools for Adverse Outcomes Associated with Preeclampsia

Determinants of risk associated with preeclampsia remain unclear.[1] Conventional wisdom and guidelines that inform preeclampsia management perform poorly when tested for their adverse outcome predictive strength.[2] Furthermore, 24-hour urine collections and dipstick evaluation for proteinuria analysis and blood pressure measurement—the diagnostic tools for preeclampsia—are unreliable indicators of preeclampsia outcomes for a variety of reasons.[3,4] New approaches to risk assessment are needed to assist in the management of pregnant women presenting with preeclampsia symptoms in order to ensure those needing definitive treatment (induction or Cesarean section) are prioritized, and to prevent unnecessary and potentially dangerous intervention when risks are low.

Several recent studies have examined multifactorial contributions to preeclampsia risk.[3,5] In this briefing, we present risk assessment tools that may have applications in low-resource settings to assist with preeclampsia management after a positive diagnosis has been made. While many single measurements have promising performance, none have sufficient performance to be used as an individual risk indicator. As an example, we highlight oxygen saturation as a variable that has one of the strongest autonomous correlations with risk. To further clarify the focus of this briefing, we make a distinction between preeclampsia screening tools, diagnostic tools, and risk management tools as follows:

- Screening. Preeclampsia screening is performed before any symptoms appear and aims to estimate the risk that the disorder will develop.
- Diagnosis. Preeclampsia diagnosis is based on symptoms, and it is made when the disease is already expressed. Diagnosis is solely based on combined hypertension with expressed proteinuria.
- Risk management. New evidence suggests correlation between a number of variables that may identify women at increased risk of adverse outcomes up to seven days before complications arise and can thereby modify direct patient care (e.g., timing of delivery, place of care), improve the design of clinical trials, and inform biomedical investigations related to preeclampsia.[3]

The table below provides a summary of two risk management tools for adverse outcomes associated with preeclampsia.

Supply Information	TECHNOLOGY/SOLUTION	
	Preeclampsia Integrated Estimate of RiSk (PIERS) multivariate analysis	**Pulse oximetry (e.g., Lifebox)**
Description	The fullPIERS model was designed as a preeclampsia outcome prediction model for use in well-resourced settings.	Lifebox is the lowest-cost detection of oxygen (O2) saturation. Designed specifically to World Health Organization (WHO) specifications for use in low-resource settings.

Characteristics applicable for low-resource settings	Recently, Dr. Peter von Dadelszen (Child and Family Institute, University of British Columbia) received a grant from the Bill & Melinda Gates Foundation to implement a comprehensive project on preeclampsia monitoring, prevention, and treatment, which includes PIERS validation in developing countries as a major component.	Designed to the following WHO specifications:
		• Robust design and durable (dropability).
		• Accurate oxygen saturation measurement (+/- 2%).
		• Audible and visual alarms:
		  ▪ Fixed 90% oxygen saturation alarm.
		  ▪ Heart rate alarm (high 120/low 60).
		  ▪ High and low alarm priorities.
		  ▪ Low battery alarm.
		• Pulse waveform display.
		• Variable pulse tone (lower saturation, deeper tone).
		• Numeric displays for oxygen saturation and pulse rate.
		• Ergonomic display.
		• Mains electrical supply with a rechargeable battery.

Developer and/or manufacturer	University of British Columbia (Canada).	Acare Technology Co., Ltd. (Taiwan).
Status	Study in well-resourced countries is complete and results published. This fullPIERS model can identify women at increased risk of adverse outcomes up to seven days before complications arise and can thereby modify direct patient care (e.g., timing of delivery, place of care), improve the design of clinical trials, and inform biomedical investigations related to preeclampsia. A study took place in Fiji, Pakistan, South Africa, and Uganda. Study completion was scheduled for 2011. Awaiting results.	Commercialized and distributed through Lifebox Global Not-For-Profit.
Efficacy/ effectiveness	Stratification identified that for the highest-risk group (4% of the population tested), the true positive rate of the test is 44% and the false positive rate is 1.6%.	SpO2 successfully predicted adverse maternal outcomes. The area under the receiver-operator characteristic curve (AUC ROC) was 0.71 (95% Confidence Interval [CI] 0.65 to 0.77). Combining the symptoms of chest pain and/or dyspnea with pulse oximetry improved this predictive ability (AUC ROC 0.73; 95% CI 0.67 to 0.78). When SpO2 was stratified into risk groups using inflection points on the ROC curve, the highest-risk group (SpO2 90% to 93%) had an odds ratio of 18.1 (95% CI 8.2 to 40.2) for all outcomes within 48 hours when compared with the baseline group (SpO2 98% to 100%).[6]

Supply Information	TECHNOLOGY/SOLUTION	
	Preeclampsia Integrated Estimate of RiSk (PIERS) multivariate analysis	**Pulse oximetry (e.g., Lifebox)**
Manufacturing quality and capacity	Not applicable. This is a model, not a device.	The WHO-audited manufacturer meets all requirements and is capable of scaling to meet need.
Intellectual property ownership	Not applicable. This is a model, not a device.	None.
Cost and cost drivers	No data available.	Margins are low. The price of US$200 seems to be the floor for this class of noninvasive detection devices at the projected sales volumes.
Delivery/ procurement channels	No data available.	No data available.
Sustainable business models		Lifebox Global Not-For-Profit is funded in part by Smile Train. Smile Train also influences the organization through strategic executive involvement. Acare Technology Co. is assumed to make a very small profit on each sale.

Demand Information	TECHNOLOGY/SOLUTION	
	Preeclampsia Integrated Estimate of RiSk (PIERS)multivariate analysis	**Pulse oximetry (e.g., Lifebox)**
Existing demand	No data available.	Market size is driven by the number of health facilities, providers, or communities. According to Lifebox's website, the unmet need is 75,000 units, though it is not clear how this was determined. The global pulse oximetry market is substantially larger—estimated toward US$1 million unit market.
Attractiveness	No data available.	The cost of the unit and replacement probes sets a new low-cost standard for pulse oximetry, while product quality and appropriateness for low-resource settings is high.
Price sensitivity	No data available.	No data available.
Policy environment	Policy does not address risk management.	The Global Pulse Oximetry Project has increased awareness and demand for this technology.
Donors/ stakeholders	Bill & Melinda Gates Foundation.	Global Pulse Oximetry Project; Lifebox; PIERS; Smile Train; WHO.
Pre- and post-sales support	No data available.	A distribution chain for replacement probes is necessary. Initial training is minimal; no calibration is required.
Need for demand creation	No data available.	The Global Pulse Oximetry Project's advocacy has increased demand, though more advocacy is warranted.

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Delivery of Magnesium Sulfate

The World Health Organization (WHO) has identified magnesium sulfate ($MgSO_4$) as the most effective, safe, and low-cost medication for preventing and treating convulsions in severe preeclampsia and eclampsia (PE/E).[1] Despite its endorsement by WHO, $MgSO_4$ is still either underused or unavailable in many low-resource settings; even when $MgSO_4$ is used, convulsions in hospitalized women are most frequently caused by undertreatment due to a combination of provider and supply factors. To improve consistent, safe use of $MgSO_4$, the following items must be available at all levels of care[2]: $MgSO_4$[3] and a delivery system that facilitates its safe administration, calcium gluconate (the antidote for $MgSO_4$), lignocaine (for intramuscular [IM] injections), a simple treatment protocol, and job aids to assist with measuring the correct dose and deciding on the route of administration.[4] A key element of managing severe PE/E is adequate administration of $MgSO_4$ to prevent or control convulsions. The loading dose of $MgSO_4$ may be administered by continuous intravenous (IV) infusion or, alternately, by giving an IV bolus and IM doses. This is followed by four-hourly IM injections.[5] Both IV and IM administration are appropriate. IM administration of the undiluted 50 percent solution results in therapeutic plasma levels in 60 minutes, whereas IV doses will provide a therapeutic level almost immediately.

The WHO-recommended regimens are:

- Loading dose. Slow IV injection of 4 g (20 mL of 20 percent solution in saline) at a rate of 1 g/5 minutes over 5 to 20 minutes.
- Maintenance regimen (IM). Immediately after the loading dose, administer 5 g of 50 percent solution to each buttock (10 g total IM dose) as a deep IM injection. This should be followed by 5 g of 50 percent solution every 4 hours to alternate buttocks. $MgSO_4$ treatment should be continued for 24 hours after delivery or the last convulsion, whichever occurs last. IM injections should preferably be given with 1 mL of 2 percent lignocaine in the same syringe to make them less painful.
- Maintenance regimen (IV). After the loading dose, administer 1 to 2 g/hour in 100 mL of maintenance solution.

In low-resource settings, the IM maintenance regimen is usually promoted for the following reasons: (1) ease of IM injections relative to IV injections, and (2) relative safety of IM over IV doses in settings that do not have pumps to control the IV infusion.

A 2010 Cochrane review[6] identified that there are several important questions about how best to use $MgSO_4$ for women with severe PE/E. These include: (1) what is the minimum effective dose (loading and maintenance); (2) what are the advantages and disadvantages of IM and IV administration; (3) can the initial dose be safely given at community or primary health care levels before transfer to the hospital; (4) is the loading dose alone sufficient for treatment of severe PE/E; and (5) when is it best to stop treatment. To address these questions would require

large randomized trials of women with severe PE/E that compare alternative regimens and assess the comparative effects on mortality, serious morbidity, adverse effects, and use of hospital resources for both the women and their babies.

The two tables below examine various options for $MgSO_4$ delivery.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Description	This is the standard of care at all levels of the health care system; it uses commodity medical technologies. The IM regimen is the most affordable and is widely used in low-resource settings.	This is a readily available delivery method for continuous IV. It consists of an IV bag and a stand and relies on gravity to administer the $MgSO_4$ dose. There is potential to augment the function with a control valve currently under development at Rice University.	This technology can make administration easier and safer, as the Springfusor® limits the rate of administration. Springfusor® is available in 10 mL and 30 mL versions. This technology requires no batteries.	This technology uses a proprietary, expandable polymer for continuous or bolus drug delivery. The device consists of a plastic case, a bag (container) for the drug, and an expandable polymer. The dosage and application method can be programmable at the factory or at the point-of-care (via a user interface installed in a computer). This device is currently designed as a single-use, disposable device to deliver narcotics for pain management.	This is the standard of care in the United States.	The Ansyr® Syringe offers one-piece, polypropylene plastic construction and a needle-free luer lock tip. An extensive portfolio of emergency medications is available. The flexible luer lock system makes it easy to connect to any valve, or to add a needle or blunt tip. The Ansyr® Syringe is prefilled.
Characteristics applicable for low-resource settings	Uses commodity technologies; therefore, a unique supply specific to preeclampsia (PE) is not required.	Electricity free. Simpler user interface than IV injection.	Can run with no power source. Easier and safer since the administration rate is tightly controlled.	Can run with no power source. Easier and safer since there is no need for mixing and the administration rate is limited. Specifications can be modified for use in low-resource settings, including making the device semi-disposable for cost reduction.	Needs electricity or another power source. Prohibitive cost.	Easier and safer since this is prefilled.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Developer and/or manufacturer	This is a generic technology and has many manufacturers.	This is a generic technology and has many manufacturers.	There are multiple elastomer- and spring-based pumps. One example is the Springfusor® made by Go Medical Industries Pty., Ltd. (WA, Australia).[7]	Medipacs (CA, USA).	There are various devices and manufacturers. For example, the SIGMA Spectrum Infusion Pump manufactured by SIGMA International, LLC, and commercialized by Baxter International.	Hospira Ansyr® (Hospira Accessories Technologies).[8]
Status	Commercialized.	Commercialized.	This technology has been commercialized with US Food and Drug Administration (USFDA) approval, CE Mark, and Therapeutic Goods Administration regulatory approval.	This technology is in late-stage development. There are plans to file for USFDA 510k clearance within a year. Regulatory hurdles are significant if this is a prefill device.	Commercialized.	Commercialized.
Efficacy/ effectiveness	This is a generic technology and is proven to be safe.	This is a generic technology and is proven to be safe.	No data available.	No data available.	This is the standard of care in the United States and is proven to be safe.	This technology should have effectiveness on par with any other delivery regimen but removes user dependence and thus improves safety.
Manufacturing quality and capacity	This technology has numerous manufacturers, so scale can be easily achieved to meet demand.	This technology has numerous manufacturers, so scale can be easily achieved to meet demand.	Go Medical has manufacturing facilities in Australia, Europe, and Asia and an established global distribution network.[7]	Medipacs is a start-up company with series-A funding. Ability to meet global demand is unclear. They will likely need to partner with a manufacturing facility.	Because of prohibitive cost, it may not be appropriate for use in low-resource settings.	Hospira is the global market leader for generic injectable pharmaceuticals, so they could easily scale to demand.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Intellectual property (IP) ownership	None.	None.	Many of the available technologies are off-patent or nearing the end of patent terms.	Uses a proprietary, expandable polymer.	None. IP is not as much a barrier to entry in this market as is the expected low return on investment.	Proprietary.
Cost and cost drivers	The cost is approximately US$1 for single use.	The cost of this device is approximately US$20.	The cost is approximately US$20. The device can be reused indefinitely on different patients; however, flow control tubing needs to be replaced after each use.	The cost is approximately US$20.[9] The device is made of low-cost components for single use.	The cost is approximately US$2,500.	Expected to add considerable cost to each successfully treated individual. Estimated prefilled cartridge costs are as much as US$0.25 based on PATH experience. Contributed costs can raise overall cost by an order of magnitude. Both a willingness to pay and a cost-effectiveness analysis are strongly recommended to justify further research and development.
Delivery/ procurement channels	Clinic-based delivery.	Clinic-based delivery.	Clinic-based delivery.	Clinic-based delivery.	Clinic-based delivery.	Clinic-based delivery.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	Gravity-fed IV bag and stand (IV)	Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump	Programmable non-mechanical IV infusion pump	Programmable electronic infusion pump (IV)	$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags
Sustainable business models	Exist.	Exist.	Current device consumable costs seem to be too high, as the contributed cost of infusor flow control tubing can add more than US$1 to a US$0.05 injection. This needs to be looked at more closely.	This device can deliver a variety of medications, such as biologics, insulin, hormones, fertility drugs, anti-coagulation drugs, and pain medication, thereby making the potential market size of the product quite large.	This technology exists in different markets. There may be too many hurdles to overcome to build a sustainable, affordable supply at the lowest levels of the health care system. This technology is more appropriate for national hospitals, where the device could be used for multiple indications—not just PE/eclampsia emergencies.	More information is needed to justify this technology. This will likely require donor-driven clinical evidence for a simplified dose regimen. It is possible there will be considerable donor investment prior to establishing a supply-side return on investment-driven sustainability.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Existing demand	PE/E market size is driven by the number of women with severe PE/E. With new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.	PE/E market size is driven by the number of women with severe PE/E. With new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.	PE/E market size is driven by the number of women with severe PE/E. With new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.	PE/E market size is driven by the number of women with severe PE/E. With new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.	PE/E market size is driven by the number of women with severe PE/E. With t new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.	PE/E market size is driven by the number of women with severe PE/E. With new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the devices can deliver any drug/vaccine, the market size would be much larger and would be driven by the number of IV or IM injections.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Attractiveness	This technology requires somewhat complicated preparation of 50 percent and 20 percent from available $MgSO_4$ preparations, and addition of lignocaine to the $MgSO_4$ solution to reduce pain from the injection.	The health worker prepares the IV bag by mixing a correct $MgSO_4$ dose regimen for the IV maintenance dose, which requires careful calculations of drops per minute based on the drip set used (10, 15, 20, or 60 drops per mL) and strength of the $MgSO_4$ solution.	In India, trials showed reduced side effects associated with $MgSO_4$ and that this device is highly acceptable to women. The trial compared manually administered IV loading dose followed by maintenance therapy IM via syringe with loading dose and maintenance therapy using IV infusion by Springfusor®.[10] Manual administration of the loading dose caused significantly more side effects.	This is a new product still under development. Significant complexity may contribute to higher than expected costs, as the device has a microprocessor, a reservoir for the drug, a printed circuit board, and the proprietary polymer, which acts as the motor to push the drug out of the reservoir as it precisely expands, gradually displacing the drug.	This device is completely automated and precise. This is overkill for $MgSO_4$, which has a wide therapeutic window.	This technology is easier and safer since there is no need for mixing.
Price sensitivity	Saturated market. Low elasticity.	Saturated market. Low elasticity.	Not determined.	This is a niche product and could be very attractive within the niche: there is high value, high price; generic pain medications and chemo are covered by insurance.	Several big companies in this market; customers have choices.	Not determined.
Policy environment	Consistent with WHO guidelines.	Consistent with WHO guidelines.	Consistent with WHO guidelines.	This device would be better suited to a single-dose regimen.	This technology is the most flexible.	A simpler dosing regimen needs to be established before this looks attractive.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Donors/ stakeholders	International standard of care.	International standard of care.	Gynuity.	Received US$4.6 million in grant funds and angel investor money.[11] Medipacs received the Association of University Research Parks' Innovation Award for 2009. The National Science Foundation provided a grant of US$700,000 for development.	None. Cost prohibitive in developing countries.	The University of British Columbia and Jhpiego are also investigating this technology.
Pre- and post-sales support	No support provided. A simple dosing calculator job aid would help to minimize errors. There is no calibration and no maintenance.	Requires the provider to manually count drops per minute to regulate the drip rate and achieve the therapeutic dose. Speed of infusion could change based on the patient's position. Potential for either underdosing or overdosing the patient. A simple dosing calculator job aid would help and minimize errors. This technology requires calibration.	No support provided. A simple dosing calculator job aid would help and minimize errors. No calibration required, as flow control tubes are precalibrated. Minimal training required.	Minimal training required. Prefill eliminates user complexity and errors.	Requires calibration.	Requires the provider to manually count drops per minute to regulate the drip rate and achieve the therapeutic dose. Speed of infusion could change based on the patient's position. Potential for either underdosing or overdosing the patient. Prefill eliminates user complexity and errors.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Syringe for intramuscular (IM) or manual intravenous (IV) injection	**Gravity-fed IV bag and stand (IV)**	**Electricity-free infusion pump, such as the Springfusor® (IV) syringe infusion pump**	**Programmable non-mechanical IV infusion pump**	**Programmable electronic infusion pump (IV)**	**$MgSO_4$ prefilled ready-to-use premixes for syringes and IV bags**
Need for demand creation	90 percent Essential Drugs List (EDL) coverage for the drug does not ensure 90 percent coverage for consumables. Vertical supply channels can create a mismatch between drug availability and delivery method consistency and availability—thus leading to dose errors.	90 percent EDL coverage for the drug does not ensure 90 percent coverage for consumables. Vertical supply channels can create a mismatch between drug availability and delivery method consistency and availability—thus leading to dose errors.	No current demand. Simplified dose regimen would help.	No current demand. Simplified dose regimen would help.	Not appropriate for the lowest levels of the health system.	No current demand. Simplified dose regimen would help.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2			
	Rectal suppository	**Preeclampsia/eclampsia (PE/E) treatment kit**	**mHealth application for dilution and dosing of $MgSO_4$**	**Animated game for correct dose/dilution uses**
Description	Early concept. The feasibility of using rectal suppositories in women who are laboring and giving birth has not been tested; expulsion may be an issue. This technology has the potential to simplify dosing, provide a less painful delivery method, and allow use at lower levels of care.	Kits could contain[1] (1) calcium carbonate (antidote); (2) job aids to demonstrate dilution and decide on dose; (3) a simple monitoring sheet to record pulse, blood pressure (BP), respirations, urine output, proteinuria, reflexes, fetal heart rate, and administration of the drug; (4) a reliable BP measuring device, stethoscope, and fetal stethoscope; (5) reflex hammer; (6) urinary collection system; (7) dipsticks to measure proteinuria; (8) timing device with a second hand; and (9) infection prevention and injection safety supplies.	PATH and the University of Washington (UW) are currently developing an application that could be modified in various forms, such as a simple paper dosing wheel or a computer- or mobile phone-based dosing calculator.	Jhpiego developed an animated game to teach providers correct dose/dilution combinations.
Characteristics applicable for low-resource settings	Zero delivery technologies required.	Eliminates problems with the vertical supply system.	Digitalization of dilution and dosing calculations running on a mobile device provide frontline health workers who do not regularly see complications as a result of eclampsia the confidence to do complicated calculations for appropriate use of $MgSO_4$.	Interactive.
Developer and/or manufacturer	Early concept; no data available.	Local variations of kits exist.	PATH/UW.	Jhpiego.
Status	Early concept.	Local variations of kits exist.	Early development.	Beta prototype.
Efficacy/ effectiveness	Early concept; no data available.	Some case studies have indicated improved compliance with the kit.	Researchers have demonstrated that the use of an electronic checklist developed to consistently prompt clinicians to provide comprehensive discharge instructions showed significant improvement, from 37 percent to 93 percent in instruction delivery.[12] No studies have been conducted examining the use of digital guidelines on $MgSO_4$ usage.	Not determined.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2			
	Rectal suppository	**Preeclampsia/eclampsia (PE/E) treatment kit**	**mHealth application for dilution and dosing of $MgSO_4$**	**Animated game for correct dose/dilution uses**
Manufacturing quality and capacity	Early concept; no data available.	Additional costs are associated with assembly and waste when supplies are not used and the kit needs to be restocked or disposed.	No data available at this time.	Simple phone application. Very low manufacturing barriers.
Intellectual property ownership	Early concept; no data available.	None.	Leveraging the open-source Open Data Kit platform developed by UW and Google.	Not determined. Code belongs to Jhpeigo.
Cost and cost drivers	Early concept; no data available.	Additional costs are associated with assembly and waste when supplies are not used and the kit needs to be restocked or disposed.	Costs of the technology are variable and are driven by the level of sophistication of the tool and the level of integration. Phones can cost between US$80 and US$200. Greater costs are in training and changes to existing workflows.	Should be free. Costs associated with development and advocacy only.
Delivery/procurement channels	Standard pharma distribution.	The most cost-effective approach is the locally assembled and restocked approach.	Phones leverage off-the-shelf components that are readily available in country, as well as existing cellular networks.	Internet.
Sustainable business models	Could incentivize pharma to engage with a drug with a historically low profit margin by creating a new dosage form.	The most cost-effective approach is a locally assembled and restocked approach; therefore, the sustainable business model may be development of a facility-driven kit.	Sustainable business models are being explored broadly within the category of mHealth and clear strategies have yet to be determined.	Not determined. Suspect best suited to a free software application (i.e., no sustainable business model).

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2			
	Rectal suppository	**Preeclampsia/eclampsia (PE/E) treatment kit**	**mHealth application for dilution and dosing of $MgSO_4$**	**Animated game for correct dose/ dilution uses**
Existing demand	Market size is driven by the number of women with severe preeclampsia/eclampsia (PE/E). With the new World Health Organization (WHO) recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower. Assuming the device can deliver any drug/vaccine, the market size would be much larger. It would be driven by the number of intravenous or IM injections.	Market size is driven by the number of women with severe PE/E. With the new WHO recommendations for induction of labor, women with severe PE will be on $MgSO_4$ much longer than previously. However, if preventive supplements are used, this number would be considerably lower.	Not determined.	Not determined.
Attractiveness	Suppository methods may have cultural barriers if not standard of practice.	Wastage associate with unused kit contents.	Necessary cellular infrastructure, cost of devices (especially replacement), and dramatic changes to workflows are key barriers to use.	Requires a mobile phone.
Price sensitivity	Not determined, though comparative $MgSO_4$ dosing is <US$0.05.	Not determined, though comparative $MgSO_4$ dosing is <US$0.05.	Needs to be evaluated.	No data available.
Policy environment	Early concept; no data available.	None, though facility- or higher-level policies and standardized protocols could assist in facility-based kit development.	No current policies guide mHealth technology adoption. United States Food and Drug Administration guidelines for digital clinical support are pending, and could be adopted outside the United States, raising the regulatory hurdles for adoption and distribution of this class of software.	None.
Donors/stakeholders	Early concept, no donors or stakeholders are identified at this stage.	Early concept. PATH has had some discussions within MCHIP at this stage.	PATH (Health Innovation Portfolio).	Jhpiego.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2			
	Rectal suppository	**Preeclampsia/eclampsia (PE/E) treatment kit**	**mHealth application for dilution and dosing of $MgSO_4$**	**Animated game for correct dose/ dilution uses**
Pre- and post-sales support	Low training hurdles.	Low training hurdles.	Development of both pre- and post-sales support is necessary for the maintenance of human and technical resources. No projects have left the pilot stage where local scalable support has been demonstrated.	Anecdotal user comments suggest it may be challenging (at least initially) to understand and use.
Need for demand creation	Required.	None, though facility- or higher-level policies and standardized protocols could assist in facility-based kit demand.	One main benefit of digital guidelines is the ability to support task-shifting to lower cadres of health workers. The tool provides global standards and defines clear delineation for which services are appropriate for the health worker to provide and which should be referred.	None.

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[1] World Health Organization (WHO). *WHO Recommendations for Prevention and Treatment of Preeclampsia and Eclampsia*. Geneva: WHO; 2011.

[2] NOTE: The recommended level of health care for management of severe preeclampsia and eclampsia is in a facility with comprehensive obstetric and neonatal care capacity. Each level of the care would therefore have specific treatment guidelines—for example, initial management—intramuscular injections for the loading dose or starting the intravenous infusion would be provided at all levels of care, and ongoing management would be provided at a facility with the capacity to provide comprehensive obstetric and neonatal care services.

[3] NOTE: Promoting treatment with $MgSO_4$ assumes that $MgSO_4$ is already on the Essential Medicines List (EML) and that appropriate policies and treatment protocols promoting its correct use are in place. In countries where $MgSO_4$ is not on the EML, or appropriate policies and treatment protocols promoting its correct use are not in place, initial project activities would necessarily include work on policies and clinical standards.

[4] NOTE: To ensure safe administration of maintenance doses and ongoing management of a woman with severe preeclampsia or eclampsia, the following accompanying equipment and supplies are also needed: (1) a simple monitoring sheet to record pulse, blood pressure (BP), respirations, urine output, proteinuria, reflexes, fetal heart rate, and administration of the drug; (2) a reliable BP measuring device, stethoscope, and fetal stethoscope; (3) reflex hammer; (4) urinary collection system; (5) dipsticks to measure proteinuria; (6) timing device with a second hand; and (7) infection prevention and injection safety supplies.

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Antihypertensive Drugs

Hypertension is the most common medical problem encountered during pregnancy, complicating approximately 10% of pregnancies.[1] Preeclampsia and eclampsia account for about half of these cases worldwide.[2] Hypertensive disorders during pregnancy are classified as hypertension without proteinuria, mild preeclampsia, severe preeclampsia, and eclampsia, as described by the World Health Organization (WHO).[3]

Hypertension without proteinuria is a relatively rare cause of maternal mortality. The vast majority of the hypertension-related deaths in pregnant women are associated with both hypertension and proteinuria, with eclampsia accounting for the great majority of these maternal deaths.

An important objective in the care of a woman with severe hypertension (diastolic blood pressure [dBP] is 110 mmHg or more), with or without proteinuria, is to reduce blood pressure (BP) in order to avoid hypertensive encephalopathy, cerebral hemorrhage, placental abruption, and intrauterine growth restriction. For this reason, the aim in treating severely hypertensive women is to keep the dBP between 90 and 100 mmHg.[4] Due to the fact that available evidence on treatment of mild and moderate hypertension in pregnancy is controversial, WHO can neither recommend nor discourage use of antihypertensive drugs for their management,[2] though their treatment protocols do not include antihypertensive treatment in these cases.[1]

While the goal of treatment of hypertension in pregnancy is to reduce maternal risk, careful attention must be made not to harm the fetus. Antihypertensive medications may permit prolongation of the pregnancy and thereby improve fetal maturity, but administration of a powerful vasodilator will result in decreased intervillous blood flow. Acute falls in maternal systemic BP may thus result in fetal compromise.

There is scarce evidence on whether treating pregnant women who develop mild to moderate hypertension in pregnancy can reduce the risk of preeclampsia. Of all the antihypertensive medications available, labetalol, nifedipine, and hydralazine are most commonly recommended for acute management of severe hypertensive disorders in pregnancy. Recent research conducted by the Maternal and Child Health Integrated Program indicates hydralazine and nifedipine are the most commonly used antihypertensives in low-resource settings.[5] A systematic review of the literature has shown that labetalol is the most promising drug to achieve a protective effect. To test its effectiveness, a randomized clinical trial is ongoing in Argentinean hospitals. The tight control needed on blood-pressure management and the relative scarcity of eligible subjects makes this trial a long-lasting investment to be conducted by well-trained research teams over several years. Approximately 10% of the pilot

sample size (200 subjects) has been recruited. After the pilot phase is complete, it will be possible to assess if the study could be realistically expanded to other centers.[6]

If antihypertensive treatment is required, guidelines differ widely. WHO recommends the following: (1) women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs; (2) the choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy, in preference to others, should be based primarily on the prescribing clinician's experience with that particular drug, its cost, and local availability; and (3) diuretics, particularly thiazides, are not recommended for the prevention of preeclampsia and its complications. Despite having documented side effects (maternal hypotension and decreased blood flow to the fetus),[7] the WHO midwifery education guide recommends use of IV hydralazine for management of hypertension in pregnancy.[8] National Institute for Health and Clinical Excellence (NICE) guidelines recommend oral labetalol despite the fact that it has a narrow therapeutic window and side effects including maternal hypotension. Recent research by the Pre-eclampsia, Eclampsia, Monitoring, Prevention, and Treatment Initiative (PRE-EMPT), funded by the Bill & Melinda Gates Foundation, indicates alternative approaches including the use of two-drug therapy as well as propranolol.

In addition to building evidence that differentiates and substantiates the effectiveness and safety of the leading hypertensive drugs for use in antenatal and prenatal care, there is a need to increase access to oral dosing options through additional measures such as clear national clinical guidelines; inclusion in national formularies; and increased training on their use.

The table below provides information on the four most commonly used antihypertensive medications for managing hypertensive disorders in pregnancy.[9,10]

Supply Information	TECHNOLOGY/SOLUTION			
	Hydralazine	**Labetalol**	**Nifedipine**	**Methyldopa**
Description	Pure vasodilator. Third line for acute management intravenous (IV). Third line for refractory hypertension. Pros: Commonly available in low-resource settings; fast acting: 5 to 20 minutes. Cons: associated with more maternal and perinatal adverse effects than other drugs including maternal headache and hemodynamic instability. WHO does not recommend continuous infusion for practical and safety issues. The long duration of action, combined with difficulty in accurately monitoring infusion rates, can result in large cumulative doses and bottoming out of BP. Narrow therapeutic window.	Balanced α-ß blocker. Oral: 200 mg (weak beta effect). IV over 1 minute: 10 mg to 20 mg. Second line for acute management (IV). Second line for chronic management. Pros: none of these agents has been associated with any consistent ill effects; extensively used in pregnancy; low potential for clinical hypotension. Cons: limited availability, more expensive, potentially limited potency as an oral agent (little experience). Wide therapeutic window.	Calicium antagonist. First line for acute management. Pros: a multicenter prospective cohort study of first-trimester drug exposures reported no increase in major teratogenicity from these agents; extensively used in pregnancy (antihypertensive, tocolytic); widely available; very potent oral agent. Cons: experience with calcium antagonists is limited; headaches are a common side effect; may increase cerebral perfusion pressure; may not be cerebro-protective.	Oral: load with 500 mg, then 250 mg twice daily to maximum of 1 g three times daily. First line for chronic management. Pros: limited data suggests stable uteroplacental blood flow and fetal hemodynamics. No long-term adverse effects on development among children exposed to methyldopa in utero. Broad usage and familiarity, and widely available. Cons: causes somnolence in many individuals; limited potency; delayed onset in action (that is, slow acting 8 to 10 hours).
Characteristics applicable for low-resource settings	Commonly available in low-resource settings; fast acting: 5 to 20 minutes, though 5 mg IV format is not ideal for low-resource settings.	Availability of oral dosing and fast acting: 30 minutes.	Commonly available in low-resource settings; availability of oral dosing and fast acting: 5 to 10 minutes.	Broad usage and familiarity, and widely available.
Developer and/or manufacturer	Multiple manufacturers including brand name Apresoline manufactured by Apotex, Inc.	A number of companies manufacture generic labetalol, including (but not limited to): Sandoz, Teva Pharmaceuticals, Watson Pharmaceuticals, Eon Laboratories.	Multiple manufacturers including brand name Procardia manufactured by Pfizer.	Multiple manufacturers including brand name Aldomet manufactured by Aspin Pharmacare.
Status	Commercialized.	Commercialized.	Commercialized.	Commercialized.

Supply Information	TECHNOLOGY/SOLUTION			
	Hydralazine	Labetalol	Nifedipine	Methyldopa
Efficacy/ effectiveness	Data are scarce.	Systematic review indicates this is the most promising drug to achieve a protective effect; clinical trial currently in progress. Largely on IV use. Large oral doses 1600 mg to 2400 mg per day are used in the United Kingdom.	Data are scarce.	Data are scarce.
Manufacturing quality and capacity	Hypertension in pregnant women is a small market in comparison to the overall hypertensive drug market. Therefore, scale to meet demand can be easily achieved. Low barriers to entry as the pharmacopeia standards are publicly available, and there are no intellectual property (IP) hurdles. Due to applicability of antihypertensives for various markets, there are vast economies of scale allowing for low production costs.	Hypertension in pregnant women is a small market in comparison to the overall hypertensive drug market. Therefore, scale to meet demand can be easily achieved. Low barriers to entry as the pharmacopeia standards are publicly available, and there are no IP hurdles. Due to applicability of antihypertensives for various markets, there are vast economies of scale allowing for low production costs.	Hypertension in pregnant women is a small market in comparison to the overall hypertensive drug market. Therefore, scale to meet demand can be easily achieved. Low barriers to entry as the pharmacopeia standards are publicly available, and there are no IP hurdles. Due to applicability of antihypertensives for various markets, there are vast economies of scale allowing for low production costs.	Hypertension in pregnant women is a small market in comparison to the overall hypertensive drug market. Therefore, scale to meet demand can be easily achieved. Low barriers to entry as the pharmacopeia standards are publicly available, and there are no IP hurdles. Due to applicability of antihypertensives for various markets, there are vast economies of scale allowing for low production costs.
Intellectual property ownership	Generic drug; off patent.	Generic drug; off patent.	Generic drug; off patent.	Generic drug; off patent.
Cost and cost drivers	Cost is US$0.026 per tablet of 25 mg (mean public-sector price in 2007 across countries in sub-Saharan Africa).[11]	To be evaluated. Price in the United States is US$0.62 per 100-mg tablet.	Cost is US$0.097 per tablet of 20 mg (mean public-sector price in 2007 across countries in sub-Saharan Africa).[11]	Cost is US$0.034 per tablet of 250 mg (mean public-sector price in 2007 across countries in sub-Saharan Africa).[11]
Delivery/ procurement channels	Antihypertensives require someone with prescriptive authority as the choice of type of antihypertensive and dosing can be complex. Prescription occurs at a health care facility.	Antihypertensives require someone with prescriptive authority as the choice of type of antihypertensive and dosing can be complex. Prescription occurs at a health care facility.	Antihypertensives require someone with prescriptive authority as the choice of type of antihypertensive and dosing can be complex. Prescription occurs at a health care facility.	Antihypertensives require someone with prescriptive authority as the choice of type of antihypertensive and dosing can be complex. Prescription occurs at a health care facility.

Supply Information	TECHNOLOGY/SOLUTION			
	Hydralazine	Labetalol	Nifedipine	Methyldopa
Sustainable business models	Antihypertensives address multiple markets, which strengthens the sustainability of this technology. However, antihypertensives are commodity products, and, therefore, are priced with slim margins, especially due to the large number of manufacturers.	Antihypertensives address multiple markets, which strengthens the sustainability of this technology. However, antihypertensives are commodity products, and, therefore, are priced with slim margins, especially due to the large number of manufacturers.	Antihypertensives address multiple markets, which strengthens the sustainability of this technology. However, antihypertensives are commodity products, and, therefore, are priced with slim margins, especially due to the large number of manufacturers.	Antihypertensives address multiple markets, which strengthens the sustainability of this technology. However, antihypertensives are commodity products, and, therefore, are priced with slim margins, especially due to the large number of manufacturers.

Demand Information	TECHNOLOGY/SOLUTION			
	Hydralazine	Labeltolol	Nifedipine	Methyldopa
Existing demand	Market size driven by number of adults with hypertension (not just pregnant and postpartum women with chronic hypertension, gestational hypertension, severe preeclampsia and eclampsia).	Market size driven by number of adults with hypertension (not just pregnant and postpartum women with chronic hypertension, gestational hypertension, severe preeclampsia and eclampsia).	Market size driven by number of adults with hypertension (not just pregnant and postpartum women with chronic hypertension, gestational hypertension, severe preeclampsia and eclampsia).	Market size driven by number of adults with hypertension (not just pregnant and postpartum women with chronic hypertension, gestational hypertension, severe preeclampsia and eclampsia).
Attractiveness	Adverse drug events (ADEs), many of which are dose related such as dizziness, headaches, constipation, low energy, or sedation. While these may be seen as minor, they can greatly interfere with normal functioning, which many patients find unacceptable.	ADEs, many of which are dose related such as dizziness, headaches, constipation, low energy, or sedation. While these may be seen as minor, they can greatly interfere with normal functioning, which many patients find unacceptable.	ADEs, many of which are dose related such as dizziness, headaches, constipation, low energy, or sedation. While these may be seen as minor, they can greatly interfere with normal functioning, which many patients find unacceptable.	ADEs, many of which are dose related such as dizziness, headaches, constipation, low energy, or sedation. While these may be seen as minor, they can greatly interfere with normal functioning, which many patients find unacceptable.
Price sensitivity	To be evaluated. Would be interesting to see how price affects the choice of which antihypertensive providers use.	To be evaluated. Would be interesting to see how price affects the choice of which antihypertensive providers use.	To be evaluated. Would be interesting to see how price affects the choice of which antihypertensive providers use.	To be evaluated. Would be interesting to see how price affects the choice of which antihypertensive providers use.
Policy environment	As mentioned above, guidelines (WHO, NICE, midwifery education) differ widely causing confusion for providers.	As mentioned above, guidelines (WHO, NICE, midwifery education) differ widely causing confusion for providers.	As mentioned above, guidelines (WHO, NICE, midwifery education) differ widely causing confusion for providers.	As mentioned above, guidelines (WHO, NICE, midwifery education) differ widely causing confusion for providers.

Demand Information	TECHNOLOGY/SOLUTION			
	Hydralazine	**Labeltolol**	**Nifedipine**	**Methyldopa**
Donors/ stakeholders	WHO has set guidelines; the Gates Foundation has funded research conducted by PRE-EMPT for evaluating alternative approaches such as two-drug therapy and propranolol.	WHO has set guidelines; the Gates Foundation has funded research conducted by PRE-EMPT for evaluating alternative approaches such as two-drug therapy and propranolol.	WHO has set guidelines; the Gates Foundation has funded research conducted by PRE-EMPT for evaluating alternative approaches such as two-drug therapy and propranolol.	WHO has set guidelines; the Gates Foundation has funded research conducted by PRE-EMPT for evaluating alternative approaches such as two-drug therapy and propranolol.
Pre- and post-sales support	There is a need for clear protocols and how to address stock-outs. Dosing is complicated. Doses need to be increased until the therapeutic level is reached. If the BP is not well controlled with one antihypertensive, either a second one is added or the drug is changed. There is an inadequacy of providers' explanations to patients of the importance of treating hypertension, which often is asymptomatic; expected side effects and how to manage and take this drug.	There is a need for clear protocols and how to address stock-outs. Dosing is complicated. Doses need to be increased until the therapeutic level is reached. If the BP is not well controlled with one antihypertensive, either a second one is added or the drug is changed. There is an inadequacy of providers' explanations to patients of the importance of treating hypertension, which often is asymptomatic; expected side effects and how to manage and take this drug	There is a need for clear protocols and how to address stock-outs. Dosing is complicated. Doses need to be increased until the therapeutic level is reached. If the BP is not well controlled with one antihypertensive, either a second one is added or the drug is changed. There is an inadequacy of providers' explanations to patients of the importance of treating hypertension, which often is asymptomatic; expected side effects and how to manage and take this drug	There is a need for clear protocols and how to address stock-outs. Dosing is complicated. Doses need to be increased until the therapeutic level is reached. If the BP is not well controlled with one antihypertensive, either a second one is added or the drug is changed. There is an inadequacy of providers' explanations to patients of the importance of treating hypertension, which often is asymptomatic; expected side effects and how to manage and take this drug
Need for demand creation	Demand creation should be well integrated into training programs such as by PRONTO International.	Demand creation should be well integrated into training programs such as by PRONTO International.	Demand creation should be well integrated into training programs such as by PRONTO International.	Demand creation should be well integrated into training programs such as by PRONTO International.

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