

# **ANTIHYPERTENSIVE MEDICINES AND BLOOD PRESSURE DEVICES:**

## **A LANDSCAPE ASSESSMENT OF ACCESS TO ESSENTIAL SUPPLIES FOR TREATMENT OF HYPERTENSIVE DISORDERS OF PREGNANCY IN THREE COUNTRIES**

December 2019

# TABLE OF CONTENTS

<b>1. INTRODUCTION</b> .....	4
<b>2. METHODOLOGY</b> .....	5
<b>3. BLOOD PRESSURE DEVICES</b> .....	7
<b>4. ANTIHYPERTENSIVE MEDICINE</b> .....	10
<b>5. CONCLUSION</b> .....	21
<b>6. APPENDICES</b> .....	22
6.1 Appendix I. List of documents reviewed	
6.2 Appendix II. List of stakeholders consulted	
6.3 Appendix III. Description of facility survey study design	
<b>7. CITATIONS</b> .....	32

# CONTRIBUTORS

## **AUTHORS:**

Hillary Bracken, Manuel Bousiéquez, Laura Frye

## **ACKNOWLEDGEMENTS:**

Gynuity Health Projects would like to thank the following individuals for their contributions:

Dr. Alka Barua (independent consultant), Dr. Sam Ononge (Makerere University), Esther Ssebyala (Global Health Uganda), Leticia Iguma (Global Health Uganda), Dr. Satish Gogulwar (Amhi Amchya Arogyasath), Manuel Urbina (INSAD), Mónica González (INSAD) and José Luis Palma (INSAD), government officials in the jurisdictions where the fieldwork was undertaken and all the individuals working on maternal health issues who took the time to speak with us.

Peggy Alevrontas and Melanie Peña (Gynuity Health Projects) assisted with the formatting of the final report.



Support for this project was funded by PATH in its capacity as the Secretariat of the Reproductive Health Supplies Coalition. The views expressed by the authors do not necessarily reflect the views of the Reproductive Health Supplies Coalition or PATH.

## 1. INTRODUCTION

Hypertensive disorders of pregnancy (HDP) remain a significant cause of maternal and fetal mortality and morbidity worldwide including pre-eclampsia/eclampsia, pre-eclampsia superimposed on chronic hypertension, and gestational hypertension. Administration of antihypertensive medicines can reduce the risk of maternal stroke or cerebrovascular events that occur with severe hypertension in pregnancy (a systolic blood pressure  $\geq 160$  or diastolic blood pressure  $\geq 110$  mm Hg). Antihypertensive drugs may also be used for treatment of other hypertensive disorders during pregnancy including chronic hypertension (i.e. pre-existing hypertension).

While it is well established that routine measurement of blood pressure (BP) and use of antihypertensive medicine can reduce serious maternal complications, there is limited evidence about how or whether national policies, standards, guidelines and procurement practices create an enabling environment for the diagnosis and treatment of HDP. Thus, the goal of this project was to assess the readiness of primary and secondary health facilities to diagnose, monitor and treat women with pre-eclampsia and eclampsia and other HDP and to identify gaps in equipment, medicines and policy and procurement practices that may pose barriers to recommended management.

The specific objectives of this project were to:

1. Assess national standards and guidelines for (a) the diagnosis, monitoring and treatment of severe hypertension in pregnancy and (b) the procurement and supply of blood pressure monitoring devices and the most commonly used antihypertensive medicines for treatment of severe hypertension in pregnancy in three countries (Uganda, Mexico and India).
2. Measure the availability, source, cost and procurement process of blood pressure devices and medicines for treatment of severe hypertension in pregnancy (nifedipine, labetalol, methyldopa and hydralazine) at public sector health care facilities and private sector medicine outlets in two districts or divisions in three countries (Uganda, Mexico and India).

## 2. METHODOLOGY

Gynuity selected three countries (Uganda, Mexico and India) for a focused assessment of the availability of essential supplies for the management and treatment of hypertensive disorders of pregnancy (specifically, antihypertensive medicines and blood pressure devices). The landscaping exercise employed a mixed methods approach and collected global, national and sub-national data from three sources: document reviews, in-depth stakeholder interviews, and health facility readiness assessments.

### Document Review

Gynuity, in collaboration with local partners, collected qualitative and quantitative data from a review of available documents in each country. A full list of the documents reviewed appears in **Appendix 1**. Documents included the following:

- Global and national diagnosis, management and treatment guidelines for severe hypertension in pregnancy, pre-eclampsia/eclampsia and other HDP
- Government documents on health system structure, drug and device registration and public procurement agency practices
- White-papers and published research on the availability and quality of antihypertensive medicines and blood pressure devices, forthcoming product innovations, and interventions to improve the quality of preeclampsia care in each country

### In-depth Interviews

In each country we also conducted in-depth interviews with key stakeholders including government health sector officials, members of professional medical societies and non-governmental organizations and researchers working on maternal health. In-depth interviews were conducted either over the phone or in-person with a total of 38 (India: 12; Uganda:14; Mexico:12 ) stakeholders. A full list of the key stakeholders interviewed appears in **Appendix 2**.

### Health Facility Assessment

In collaboration with research partners in each country, we conducted a cross-sectional mixed methods facility survey in a sub-sample of health care facilities and private pharmacies in two districts in each country (Uganda, Mexico and India). The aim of the survey was to assess facility readiness to provide care for hypertensive disorders of pregnancy. We also assessed the availability and cost of antihypertensive medicines and magnesium sulfate in local pharmacies in order to better understand patients' ability to access these essential medicines in the event of drug stock-outs at the health care facility. A diagram describing the study design may be found in **Appendix 3**.

The study districts were selected in collaboration with our local research partners and included one high resource district where we anticipated access to essential medicines would be good and a second low-resource district where access to care would be more challenging. The number of facilities sampled was limited by time and resources but, where possible, we attempted to sample at least 40% of facilities in the district. The sample was neither comprehensive nor exhaustive but meant to highlight issues for further research and attention by key stakeholders and implementing partners in each country. In total, the assessment included 48 public sector health care facilities, 24 private maternity homes (India) and 181 private pharmacies across the three countries.

## UGANDA

In Uganda, the survey was conducted in Butambala and Masindi regions by partners and Global Health Uganda. We sampled a total of 32 facilities in these two regions: 17 level II centers, 12 level III centers, 1 level IV center and 2 hospitals. This sample represents 50% of all operable government or mission facilities in these two regions. The survey team also surveyed 32 private pharmacies located in close proximity to each health facility

## INDIA

In India, Amhi Amchya Arogyasathi (AAA), a Nagpur-based NGO, conducted the facility based survey. The survey was conducted in Gadchiroli and Nagpur districts in Maharashtra state. Nagpur district is a better performing district according to Government of India reproductive health indicators and is home to the Government Medical College, Nagpur. Gadchiroli is a tribal and poor performing district located 170 kilometers away from Nagpur city. We were unable to obtain government approval to conduct the survey in public sector facilities in the two districts. Instead, we conducted the survey in a sample of private maternity homes in the two districts. The final sample included 24 private maternity centers (Nagpur: 15 centers; Gadchiroli: 9 facilities) or approximately 40% of private maternity homes in the districts (n=60). The team also assessed the availability of essential medicines in the two closest pharmacies to these medical facilities (Nagpur: 27 pharmacies; Gadchiroli: 26 pharmacies).

## MEXICO

In Mexico, we contracted with the Investigación en Salud y Demografía (INSAD) in Mexico City for the facility survey. The survey was conducted in the municipality of Azcapotzalco in Mexico City, an adequately-resourced district which includes a maternity hospital and 14 primary care units (PCU) and in Ecatepec in the nearby State of Mexico. Ecatepec represents a marginalized area known for its insufficiency of public health services. In Ecatepec there are 2 general Hospitals and 22 PCUs. The survey included a total of 40% of the identified medical units for each jurisdiction including the maternity hospital and 5 PCUs in Azcapotzalco and the two general hospitals and 8 PCU in Ecatepec. In total, INSAD visited 16 health facilities and 96 private pharmacies, 60 of which were located near to medical units in Ecatepec and the remaining 36 in Azcapotzalco.

### 3. BLOOD PRESSURE DEVICES

Blood pressure monitoring is a key component of antenatal and postnatal care. The World Health Organization (WHO) antenatal care guidelines recommend 8 antenatal care visits with blood pressure and proteinuria measured at each visit.<sup>1</sup> More frequent monitoring of blood pressure is recommended for women with elevated or poorly controlled blood pressure, either in the facility or at home.<sup>2</sup> Postpartum guidelines recommend that blood pressure be measured shortly after birth<sup>3</sup> and if normal, a second BP should be taken within 6 hours. As during the antenatal period, more frequent monitoring is warranted in cases with elevated blood pressure.

A number of different types of devices are currently available for measuring blood pressure. Manual devices require manual inflation, auscultatory skills, and observer recording and are subject to human error. Mercury sphygmomanometer devices have historically been the gold standard device for blood pressure measurement. However, these devices present significant environmental and safety hazards if broken and are no longer recommended for use in routine healthcare settings by the WHO and other international professional bodies.<sup>4</sup> Aneroid devices are mechanical but must be routinely calibrated to avoid erroneous reading. Automated (e.g. oscillometric) devices detect blood movement through the brachial artery and convert movements into a digital reading. Automated devices do not require a stethoscope and may eliminate human error. However, automated devices can yield inconsistent readings if not correctly validated and, of course, will not function if a power source (e.g. battery or electricity) is unavailable.

The International Organization for Standardization (ISO) maintains specifications for automated and non-automated BP devices.<sup>5</sup> However, few countries require that an individual device be validated for marketing. In most countries, devices may be marketed because they are similar to another device approved by a national regulatory authority, and there is little public data on validation status of marketed devices. That said, in 2019, the ISO published new practical guidance for validation of BP devices.<sup>6</sup> The British and Irish Hypertension Society (BIHS) also maintains a list of recommended (i.e. validated) and not recommended devices on their website (<https://bihsoc.org/bp-monitors/specialist-use/>). In 2019, the American Medical Association (AMA) in the United States also started working to create national list of validated blood pressure devices available in the US market.<sup>7</sup>

Because hemodynamic and vascular changes occur during pregnancy, guidelines recommend validating BP devices in pregnant women. However, a systematic review of validation studies found that while the majority of BP measurement devices included a validation protocol in pregnant women, most were significantly underpowered (i.e. included too few pregnant women).<sup>8</sup> The BIHS list currently includes only one device under 100 GBP validated for use in pregnancy: the Microlife Watch BP Home.

Several innovations seek to improve the quality of blood pressure monitoring in pregnancy. The CRADLE device is a novel vital signs alert device developed specifically for use in pregnancy in low resource settings<sup>9,10,11</sup> and is now available for sale on the Maternova website ([ww.maternova.net](http://www.maternova.net)).<sup>12</sup> The World Health Organization is also developing a cuffless BP device linked to patient record and decision making software.<sup>13</sup>

## QUALITY ASSURANCE MEASURES FOR BLOOD PRESSURE DEVICES

Our landscape assessment found **very little regulation or national policy guidance on procurement of blood pressure devices in all three project countries.** In Uganda, the National Drug Authority (NDA) monitors equipment imported for government and NGO health facilities and follows ISO and IEC guidance on medical devices. However, NDA guidance on medical device registration is still in development.<sup>14</sup> In India, BP monitors are not a notified device and thus do not require registration with the national drug authority (Drug Controller General of India). Instead, manufacturers must only obtain a No Objection Certificate (NOC) from the DCGI stating that the product does not require registration and can be imported freely.

The lack of regulation may contribute to wide variations in the quality of devices available in the market. Key informants in Uganda verified that available blood pressure devices were of variable quality. A technical expert noted that, *"I don't think we really have a problem with quality of drugs. But.. [regarding blood pressure devices]... There are many fake ones in the market. They usually break down."* Indeed, our facility survey found 22 different brands of manual and automatic devices in the 26 facilities surveyed in Uganda. Providers at the facilities confirmed that the devices were frequently inoperable: Although 80% of surveyed facilities had a working blood pressure device available on the day of the visit, nearly one-third of those devices were reported as not working for more than 15 days in last two months. A Ugandan policy maker noted: *"The issue of maintenance is still so very poor... you find that these equipment when they break, take long to be repaired, you find a hospital having maybe two working BP machines which are rotated in all the units."*



Courtesy of Jonathan Torgovnik/Getty Images Reportage

Our assessment found a greater availability of working blood pressure devices in public sector facilities in Mexico. All facilities surveyed had a working blood pressure monitoring in place, and only one device was reported missing or non-functioning for more than 15 days in the last two months. Only a few brands (n=3) of devices were found in health facilities – not surprising given that medical devices, like medicines, are procured centrally by the federal government in Mexico.

**Financing for the replacement or repair of existing equipment was a significant challenge in all three countries.** In Uganda, many HC IIIs had digital devices on site but lacked batteries rendering the device inoperable. One provider noted available batteries lasted only one month. The procurement process for replacement devices or batteries was not efficient or clear: One district health officer was unclear on how or whether untied funds could be used for purchases for BP devices and/or replacement batteries. One midwife reported that she either purchased batteries herself or requested patients purchase batteries for the device.



In India, all government health facilities from the sub-center to the tertiary care center are expected to be equipped with a fully functional blood pressure apparatus (usually manual sphygmomanometer) and a stethoscope. In case of disrepair, the health service providers can either requisition those from the central store identified for supply or purchase them locally with the untied funds availability within the facility. However, one key informant working in the public sector noted that while funds are locally available, the decentralization of the procurement process has sometimes proved challenging and resulted in stock outs in devices. The respondent noted that medical officers in charge of lower level facilities were either not at their posts and/or often slow to order and/or do not account for the days needed for supplies to reach a facility. As a result, equipment was frequent missing. A key stakeholder in Mexico also confirmed that the supply of BP devices at lower level facilities was also inadequate: *"I think the availability of supplies in large hospitals is adequate; however, the first level of attention has deficiencies, and it is the first contact and those that supposedly make the detection."*

Key stakeholders in all three countries noted ongoing national efforts to improve access to quality supplies as part of broader campaigns aimed at improving care for non-communicable diseases and general hypertension. For example, in India, the Indian Council of Medical Research ICMR launched India Hypertension Control Initiative in 2017 in 25 districts and in August 2019 expanded the effort to 100 districts. The Initiatives aims are to simplify patient care in primary care facilities, provide adequate supply of good quality medicines and blood pressure monitors and introduce comprehensive training on current based practices for healthcare workers at all levels.<sup>15</sup> However, such efforts may not necessarily address treatment of hypertension in pregnancy specifically and better efforts need to be made to highlight the importance of supplies for hypertension in pregnancy and that the blood pressure devices are essential supplies for maternal health.

## BLOOD PRESSURE DEVICES

### CHALLENGES

- Very little regulation or national policy guidance on procurement of blood pressure devices
- Financing mechanisms for replacement or repair of devices or provision of consumable supplies such as batteries unclear

### RECOMMENDATIONS

- Improve technical specifications and financing guidance for blood pressure devices
  - Provide procurement officers technical guidance and specifications on types and qualities of a 'good quality' BP device
  - Clarify whether and how replacement BP devices can be financed
- Collaborate and partner with broader efforts to improve access to blood pressure devices as part of national and international advocacy and quality improvement programs for improving care for general hypertension and non-communicable diseases.

## 4. ANTIHYPERTENSIVE MEDICINES

The WHO recommends treatment with antihypertensive medicines (hydralazine, labetalol, nifedipine immediate-release capsules, or alpha methyldopa) for acute treatment of severe hypertension in pregnancy.<sup>16</sup> According to the WHO, choice and route of administration of an antihypertensive drug for severe hypertension during pregnancy “should be based primarily on the prescribing clinician’s experience with that particular drug and its cost and local availability, while ensuring that the medicine has no adverse fetal effect.”<sup>17</sup> Hydralazine, alpha methyldopa and nifedipine are listed in the WHO model list of essential medicines (WHO EML) (**Table 1**) and also included in many national lists of essential medicines and standard treatment guidelines. A 2013 survey of hypertensive therapies listed in 91 EMLs in 144 low and middle income countries found the following included: nifedipine (95.6%); methyldopa (93.4%); labetalol (12.1%) and hydralazine (IV) (61.5%).<sup>18</sup>

The WHO EML lists nifedipine only as a tocolytic or treatment for prevention of preterm birth rather than a treatment for severe hypertension in pregnancy (**Table 1**). This is problematic given that treatment guidelines from WHO (**Table 2**) and other professional bodies (e.g. ACOG, SGO, FIGO) recommend the use of nifedipine for treatment of severe hypertension in pregnancy. This distinction is maintained in other international guidance on priority medicines for mothers and children: For example, the Priority Medicines for Mothers and Children 2012 (WHO, UNFPA and UNICEF)<sup>19</sup> and the USAID/OFDA pharmaceutical guidance<sup>20</sup> only include hydralazine and methyldopa for the management of pregnancy induced hypertension; nifedipine is only listed as a tocolytic.

**Table 1. Antihypertensive Medicine Formulations Typically Used in Pregnancy**

Drug	WHO EML formulation and indication	Typically available formulations	Storage
<b>Methyldopa</b>	250mg tablet for acute management of <b>severe hypertension in pregnancy</b> (12.3)	250mg and 500mg tablets	Dry conditions away from sunshine and light at room temp not to exceed 25 degrees Celsius.
<b>Nifedipine</b>	Immediate release capsule 10mg for <b>antioxytotic</b> (tocolytics) (22.4)	5mg and 10mg immediate release (capsule), 10mg, 20mg and 30mg modified release (retard tablet) and 20mg or 30mg extended release (XR) formulations	
<b>Labetalol</b>	Not listed	200mg tablet and ampoule	
<b>Hydralazine</b>	Powder for injection; 20mg (hydrochloride) in ampoule for acute management of <b>severe hypertension in pregnancy</b> (12.3)	Ampoule	

Reference: WHO Model List of Essential Medicines 21st List (2019).

WHO and other global guidelines recommend the use of nifedipine immediate release tablets for the treatment of severe hypertension in pregnancy (**Table 2**). However, as noted in Table 1, nifedipine is available in three formulations: immediate, modified and extended release. The immediate release tablet is licensed for the prophylaxis of chronic stable angina pectoris, the treatment of Raynaud's phenomenon and essential hypertension and is administered every 8 hours. The extended release (XR) and modified release (or retard) formulations of Adalat are licensed for the treatment of hypertension and prophylaxis of angina and administered once daily and twice daily, respectively. There is little data on the use of either the modified (retard) or extended release (XR) formulation for treatment of severe hypertension in pregnancy. However, one recent study testing three oral medicines for treatment of severe hypertension in pregnancy found use of the modified (retard) formulation more effective than methyldopa alone for control of blood pressure within six hours.<sup>21</sup>

**Table 2. WHO Treatment Guidelines for Acute Treatment of Severe Hypertension in Pregnancy**

Drug	Treatment guideline
<b>Methyldopa</b>	750mg oral with a repeat dose after 3h until BP goal achieved. Max dose: 3g in 24 h
<b>Nifedipine</b>	5-10mg immediate-release capsule oral with a repeat dose after 30 minutes if response is inadequate until BP goal achieved. Max dose in acute treatment setting: 30mg.
<b>Labetalol</b>	Oral: 200mg. Repeat dose after 1h until BP goal achieved. Max dose: 1200mg in 24 h. IV: 10mg IV and, if the response is inadequate after 10 minutes, then 20mg IV. Maximum total dose: 300 mg.
<b>Hydralazine (IV)</b>	5mg IV repeated every five minutes until BP goal achieved. Repeat hourly as needed or give 12.5 mg IM every two hour as needed. Max dose: 20mg in 24 hours.

Reference: *Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors* – 2nd ed (WHO, 2017). WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018. License: CC BY-NC-SA 3.0 IGO.

## THE NATIONAL ESSENTIAL MEDICINES LIST

Our review found that the national EML in the three selected countries, like the WHO EML, included multiple medicines (methyldopa, nifedipine and hydralazine) and labetalol (IV) (in India and Uganda) (**Table 3**). Generally, national procurement guidelines allowed for stocking of both oral and/or IV antihypertensive medicines at lower level centers (India: methyldopa and IV labetalol; Mexico: hydralazine and nifedipine; Uganda: methyldopa and nifedipine). While the Uganda EML considered magnesium sulfate a 'vital' drug (i.e. "used to diagnose and treat life-threatening conditions, or which are considered medicine of choice or" first line" items in their therapeutic category"), no oral antihypertensive was considered vital for stocking at any level. The three national EMLs did not specify the nifedipine formulation (i.e. immediate or retard) although dose (10mg) was specified in India and Mexico.

**Table 3. Health Facility Level for Stocking Essential Medicines as per National EML**

Drug	UGANDA	MEXICO	INDIA
Methyldopa	HC III (Essential)+higher	Secondary and tertiary	Primary, secondary and tertiary
Hydralazine	HC IV (Vital) + higher	Primary	N/A
Nifedipine	HC III (Essential)+ higher	Primary	Secondary and tertiary
Labetolol (IV)	Regional Referral (Vital) +higher	N/A	Primary, secondary and tertiary
MgSO4	HC III (Vital)+ higher	Secondary and tertiary	Secondary and tertiary

References: Uganda: EMHSLU 2016; Consejo de Salubridad Nacional: Cuadro Básico y Catálogo de Medicamentos. Edición 2017; India National Essentials Medicine List (NEML 2015)

**The inclusion of an antihypertensive drug on the EML alone may not be sufficient to encourage its use for treatment of HDP. The indication for which it is listed may, without additional clarification, prove a barrier to access.** In India, the National List of Essential Medicines (NLEM), modeled on the WHO Essential Medicine List, also only includes nifedipine as a tocolytic, a drug to treat premature labor. As a result, the NLEM 2015 only allows for the use of nifedipine at the secondary and tertiary levels; hydralazine and methyldopa, treatments for hypertension in pregnancy, are permitted to be used at the primary, secondary and tertiary levels. In Mexico, while methyldopa (250mg) and nifedipine (10mg) are both included in the national EML, only hydralazine (injectable) is listed for use in pregnancy (and specifically for preeclampsia/eclampsia management). The sub-national EML for Mexico City (SEDESA), where we conducted the facility survey, mirrors the national guideline.

National clinical guidelines can provide additional clarification of the role of specific medicines in treatment of HDP (Table 4). **However, the national clinical guidelines we reviewed did not always specify the drug formulation required.** Generally, information on dosage only specified the initial and maximum dose and did not provide guidance on dose escalation protocols. **In facility surveys, providers often noted the need for additional practical guidance on how to apply and implement both national and international treatment guidelines in their practice.**

**Table 4. National Treatment Guidelines for Treatment of Severe Hypertension in Pregnancy**

Drug	UGANDA	MEXICO	INDIA
<b>Diagnostic criteria for severe hypertension in pregnancy</b>	<p>* No specific diagnostic criteria for severe hypertension alone listed.</p> <p><b>Severe Preeclampsia:</b> Systolic BP <math>\geq</math> 160 mmHg and diastolic BP <math>\geq</math> 110 and <math>\geq</math>1+ proteinuria or any degree of hypertension with organ dysfunction (renal dysfunction, raised liver enzymes, thrombocytopenia)</p>	Systolic BP $\geq$ 160mmHg and/or Diastolic BP $\geq$ 110mmHg after 20 GA of pregnancy and up to 12 weeks post-partum.	Systolic BP $\geq$ 160 mmHg and Diastolic BP $\geq$ 110 mmHg
<b>Antihypertensive drug treatment guideline</b>	<p><b>ORAL</b></p> <p><b>Nifedipine</b> 20mg-40mg every 12 hours until delivery (HC3 and HC4)</p> <p><b>IV</b></p> <p><b>Hydralazine</b> 5mg IV bolus every 30 min until dBP&lt;100Hg OR (HC4 only)</p> <p><b>Labetalol</b> 20mg IV (Regional referral hospital only)</p>	<p><b>ORAL</b></p> <p><b>Nifedipine</b> 10 mg oral, every 10-15 min. Maximum dose: 50 mg</p> <p><b>IV</b></p> <p><b>Labetalol</b> 20 mg in bolus up to 40 mg every 10-15 min or through infusion @ 1-2 mg/min. Max dose: 220 mg. <i>Note: IV labetalol not registered but recommended as first line treatment.</i></p> <p><b>Hydralazine</b> 5-10 mg in bolus or through infusion @ 0.5-10 mg/hour. Max dose: 30 mg</p>	<p><b>ORAL</b></p> <p><b>Methyldopa</b> 250/500 mg 3-4x per day. Repeat every 3 hours (max 2-3 gm/day)</p> <p><b>Nifedipine</b> 5-10mg. Repeat 30 min (max 30/120mg/day)</p> <p><b>Labetalol</b> 100-200 mg every 12h (max 1200mg)</p> <p><b>IV</b></p> <p><b>Labetalol</b> 20 mg stat, 40 mg after 20 mins; increase to 80 mg (max 300 mg/day)</p> <p><b>Hydralazine</b> 5 mg IV, slowly, repeat / 5 mins OR 12.5 mg IM/ 2 hrs (max 20mg/day)</p> <p><b>IV Nitroglycerine</b> 50mg in 500ml 5% Dextrose</p>

**References:** Uganda Clinical Guidelines 2016; Mexico Clinical Practice Guideline (GPC) # IMSS-058-08 (updated 2017): Screening, Diagnosis and Treatment of Hypertensive Disorders during Pregnancy; Maternal Health Division, Department of Family Welfare, Ministry of Health & Family Welfare Government of India. 2005. *Guidelines for Pregnancy Care and Management of Common Obstetric Complications by Medical Officers.*

Despite these limitations, in both Mexico and India, clinical practice guidelines provided by the Ministry of Health have helped expand access to drugs not included in the EML for treatment of HDP. In India, nifedipine is included as an essential supply at the primary care level in India (as dictated in the Indian Public Health Standards 2016). In Mexico, nifedipine, together with hydralazine, is included at second-level and third-level health units in an obstetric Red Box (a plastic box containing relevant drugs to adequately treat preeclampsia/eclampsia, located in the Emergency Room or close to the labor and delivery room) as per the Mexico Clinical Practical Guidelines for Obstetric Triage (2016). These examples may prove helpful for other countries such as Uganda attempting to expand access beyond the scope of the national EML.

## QUALITY ASSURANCE MEASURES FOR ANTIHYPERTENSIVE MEDICINES FOR TREATMENT OF HDP

Currently there are no antihypertensive medicines included in the WHO prequalified products list. Quality-assured methyldopa and hydralazine (IV) products are available in the UNICEF and UNFPA product catalogs as of November 2019. However, prices for methyldopa 250mg tablets varied twenty-fold between the two catalogs: UNICEF: 250mg methyldopa tablets were \$3.68 USD per pack of 100 or approximately 0.04 per tablet<sup>22</sup> versus UNFPA: 250mg methyldopa tab were \$80.50 USD per pack of 100 or \$0.80 per tablet.<sup>23</sup> Prices for hydralazine hydrochloride in 2ml ampoules were listed at around \$4 USD per ampoule in both catalogs.

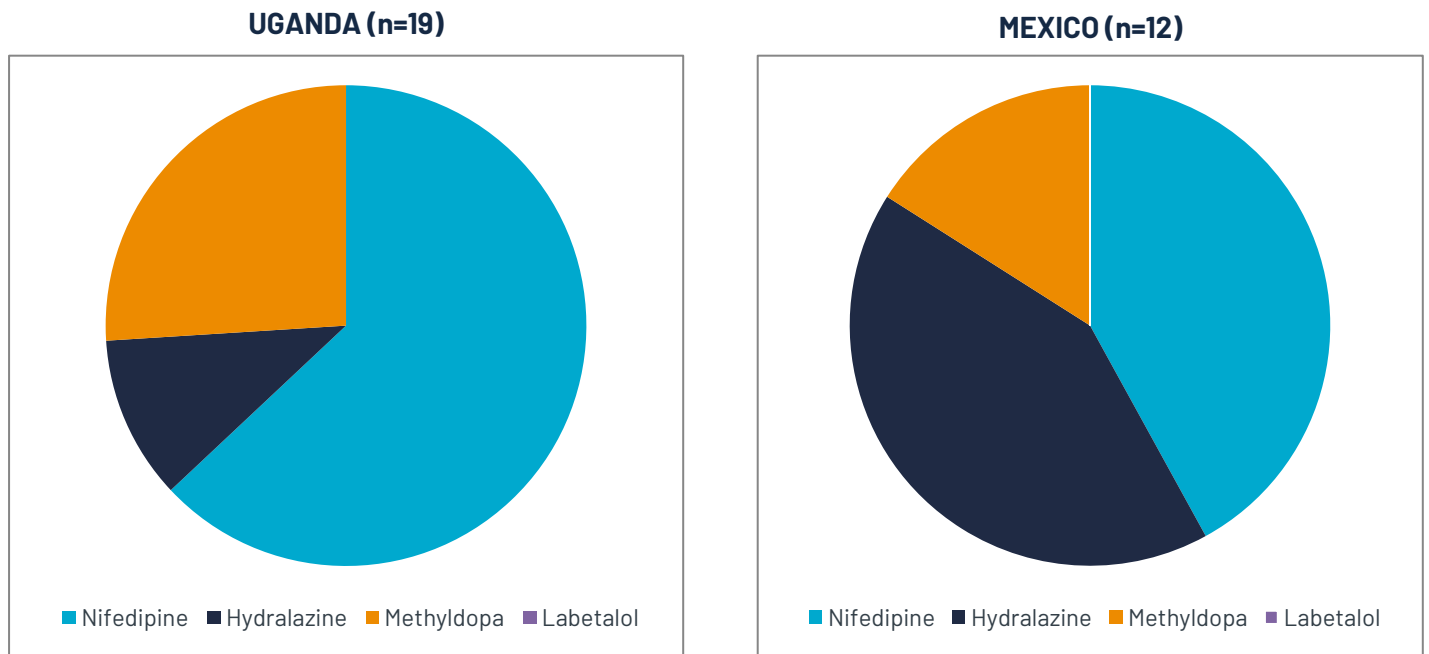
Neither nifedipine immediate release capsules 10mg nor labetalol (either IV or tablet) were included in the UN agency catalogs. Some nifedipine products have achieved stringent regulatory approval (SRA): Nifedipine 10mg immediate release capsule has been registered under the trade names Adalat (Bayer) and Procardia (Pfizer). However, the production of the immediate release formulation by Bayer has been discontinued and shortages have been reported in the UK and Canada.<sup>24</sup> Pfizer continues to market the immediate release formulation in the US. Generic formulations of the modified release or retard nifedipine formulation are more widely available, but SRA-approved generics may primarily be found in developed countries.

In Mexico and Uganda, we reviewed on-line drug registries and found registered nifedipine, hydralazine and methyldopa products (**Figure 1**). **Labetalol in either the oral or IV formulation was not registered in either country although IV labetalol was included on the Uganda EML and IV labetalol listed in the Mexico national treatment guidelines.** In Uganda, most registered products were manufactured in India and of unknown quality.

**In both Mexico and Uganda, nifedipine was the most commonly registered drug. However, both countries had few registered 10mg immediate release nifedipine products, the formulation recommended by WHO and most international treatment guidelines (Figure 2).**

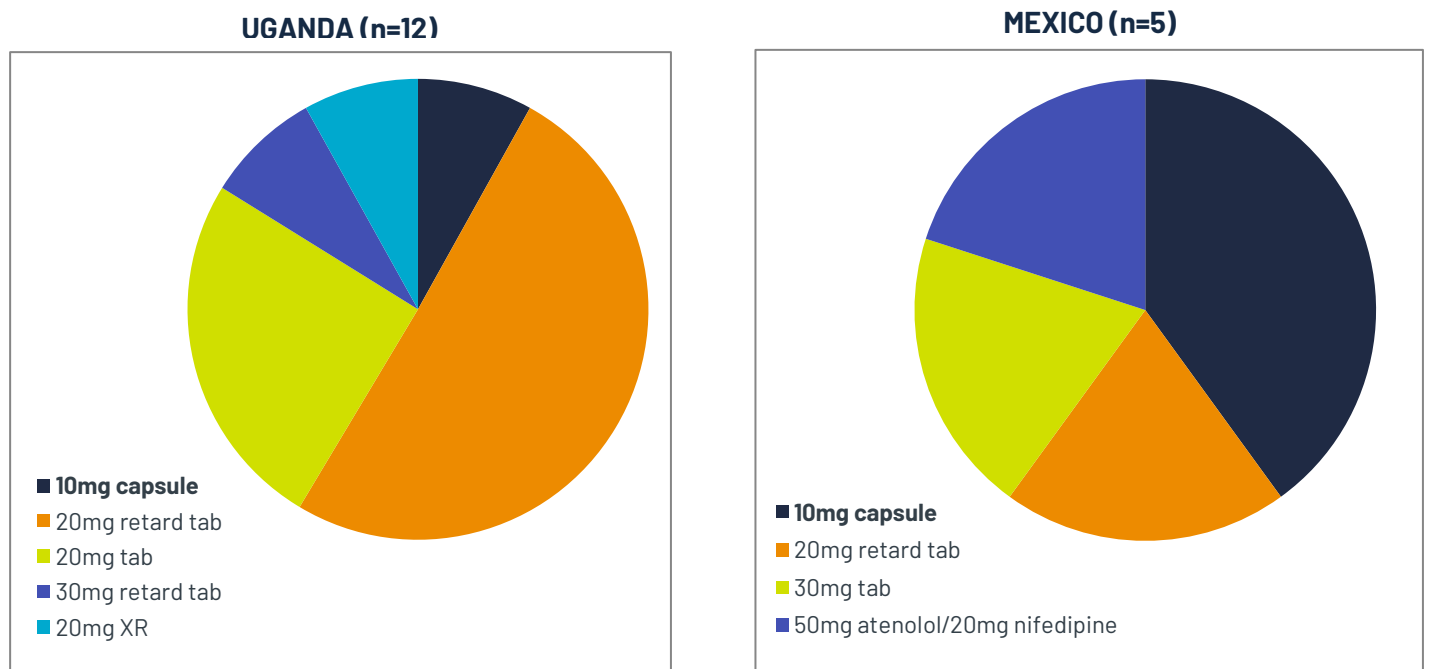
Given the large pharmaceutical industry in India, there are several nifedipine, labetalol and methyldopa products (tablet and IV) available in the market. Companies must register any drug intended for sale with national (Drug Controller General of India), regional and state-level registries and these authorities are required to maintain a list of registered products. However, none of these agencies maintain an online or publicly accessible database of registered products, so it was impossible to confirm the number of registered methyldopa, nifedipine, labetalol or hydralazine products.

**Figure 1. Registered Antihypertensive Drugs Used for HDP**



Reference: Drug Register of Uganda, Human Medicines, August 2019; Mexico: <http://tramiteselectronicos02.cofepris.gob.mx/BuscadorPublicoRegistrosSanitarios/BusquedaRegistroSanitario.aspx>. Septiembre 2019

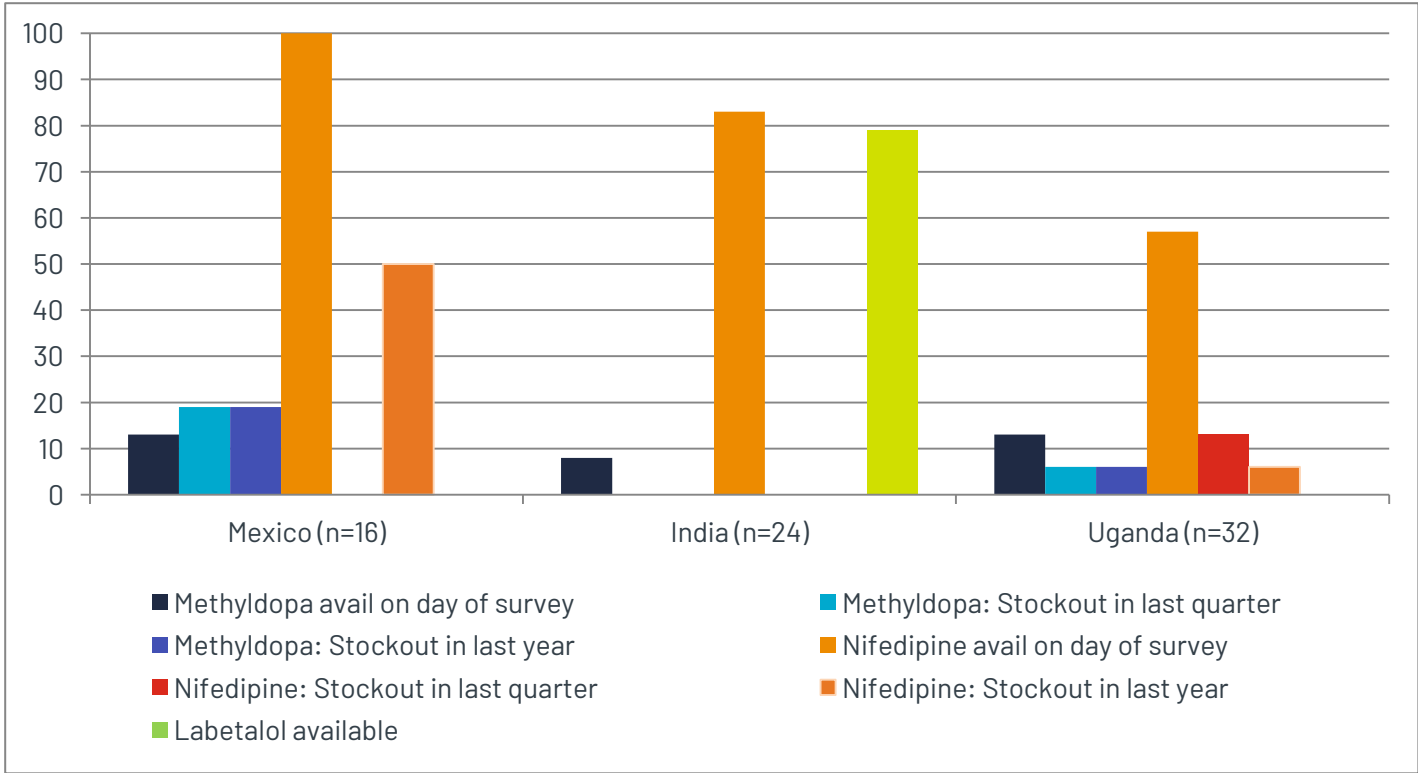
**Figure 2. Registered Nifedipine Products per National Drug Registry**



Country of manufacture of registered products: Uganda (Germany, India, Cyprus, Kenya); Mexico (Germany, India, Mexico). Reference: Drug Register of Uganda, Human Medicines, August 2019; Mexico: <http://tramiteselectronicos02.cofepris.gob.mx/BuscadorPublicoRegistrosSanitarios/BusquedaRegistroSanitario.aspx>. Septiembre 2019

### AVAILABILITY OF ANTIHYPERTENSIVE MEDICINES FOR TREATMENT OF HDP IN HEALTH FACILITIES AND NEIGHBORING PHARMACIES

We conducted a cross-sectional mixed methods facility survey to assess the availability of antihypertensive medications for treatment of HDP in health facilities in the three countries. **Our survey found that the most commonly available drug in facilities in all three countries was nifedipine (Figure 3).** IV medications were not widely available except at referral hospitals or tertiary level centers. All the districts hospitals in Uganda had hydralazine available on the day of the survey but all also reported stock outs in the last quarter and year.



**Note:** In Uganda, nifedipine was available in 93% of HCIII+ facilities. Most common formulation was 20mg retard. In India, survey conducted in private maternity homes.



***While methyldopa was listed on national EMLs as an essential medicine for treatment of hypertension in pregnancy, the drug was not consistently available at the primary and secondary care level (Mexico) or at all levels of care (Uganda) or in private sector facilities (India)***

In Uganda, methyldopa was supplied as part of a 'kit' (i.e. 3 month supply). As noted by key informants and health providers at facilities: If centers did not treat a lot of HDP patients -- either because they lacked BP monitors to assess blood pressure or because they referred patients directly to higher levels of care -- methyldopa supplies would become expired and/or procurement officers prioritized outpatient drugs for purchase. In Mexico, a key informant noted that "[Availability] is insufficient; because prequalified suppliers do not continuously supply ... The procurement process is difficult and confusing and causes delays in the supply of drugs and devices." A key informant in India noted that forecasting was very difficult given the lack of cause-specific mortality data or even HMIS data on rates of preeclampsia or eclampsia or HDP more generally in public sector facilities.

The Indian pharmaceutical landscape also creates other challenges to accessing methyldopa. Methyldopa 250mg is the only oral medicine listed in the national essential medicines list for treatment of hypertension in pregnancy. However, the essential medicine came under price control in 2015 with a result price of 0.02 USD per tablet. In response, the two major manufacturers producing the medicine stopped producing the 250mg tablet and launched a new product under a different dosage (500mg) and charged a higher retail price (.22 USD per tablet).<sup>25</sup> At the same time, one company started marketing 100mg labetalol tablets under the brand name Alphadopa-L. The result was great confusion among providers unfamiliar with either the new formulation or the new drug (labetalol) marketed with a similar name to methyldopa. The confusion coincided with widespread stockouts in both government facilities and pharmacies as the standard 250mg tablet became unavailable. Today, methyldopa is available in public facilities, although supply is somewhat erratic, but largely absent from the private sector, as confirmed by our survey of pharmacies in and around Nagpur. One key informant working in a non-governmental organization believed that broader governmental efforts to make generic drugs more available and affordable have also, in some cases, provided a disincentive for pharmaceutical companies to manufacture drugs used in maternal health, including methyldopa and hydralazine.

In contrast, nifedipine, a drug more widely used for treatment of general hypertension, was widely available in health facilities in all three countries. As suggested by the number of registered products in each country, nifedipine retard, rather nifedipine immediate release, was the most frequently available formulation in health facilities and, in India and Uganda, the 20mg tablet was most frequently available.

In Uganda and Mexico, we found that almost all products available in health facilities were registered products and most were stored appropriately and not expired. That said, the products were of unknown quality, i.e. without approval from an internationally recognized quality assurance mechanism, and future research would need to assess the quality of currently marketed products. A 2018 systematic review of studies of substandard essential medicines in LMIC did not include any studies of antihypertensive drugs.<sup>26</sup> There is some research suggestion that methyldopa may be particularly susceptible to degradation in tropical climates<sup>1</sup> but additional data is needed on both the quality of existing nifedipine and methyldopa products and the impact of different storage conditions on drug quality.

**While nifedipine was the most available antihypertensive, public sector healthcare facilities still reported stock outs of any hypertensive medicines as a significant barrier to providing high quality care.** In Uganda, providers noted that they often sent patients to nearby pharmacies to purchase drugs when drugs were not available at the healthcare facility. In order to better understand the availability and cost of drugs in the market in the three countries, we also conducted a survey of the types and prices of drugs available in pharmacies close to the selected facilities (**Table 5**). Drug availability mirrored the findings from the facility survey with nifedipine as the most available and least expensive drug. Only in Mexico did we find nifedipine immediate release capsules widely stocked.

While at least one drug was generally available, prices in pharmacies were often higher than in public facilities: In Uganda, prices in pharmacies were nearly 2 to 10 times the price in the public sector. We also found that pharmacies located in rural areas or near primary health centers in India and Uganda were less likely to stock any antihypertensive medicine. For example, in Uganda we found that in half of HCIII and HCII facilities, there was no drug shop nearby or the shop was not licensed to sell prescription medicines.

**Table 5. Availability and Mean Price (USD) of Antihypertensive Medicines in Private Chemist or Pharmacies Near Surveyed Health Facilities**

Medicine	INDIA		UGANDA		MEXICO	
	Availability (n=53)	Mean Price (range)	Availability (n=32)	Mean Price (range)	Availability (n=96)	Mean Price (range)
<b>Hydralazine</b>	0%	NA	0	NA	14%	3.80 (0.42-6.24)
<b>Nifedipine</b>	<b>58%*</b>		<b>56%#</b>		<b>96%#</b>	
5mg		0.01	0	--	4%	0.01 (0.01-0.16)
10mg		0.02	3%	0.08	74%	0.02 (0.01-0.32)
10mg retard		-	3%	0.05	0	-
20mg retard		0.03	38%	0.03 (0.01-0.11)	0	-
20mg XR		--	19%	0.05 (0.01-0.07)	0	-
30mg		--	--	--	66%	0.05 (0.01-0.16)
<b>Methyldopa</b>	<b>4% (500mg)</b>	0.09	<b>6% (250mg)</b>	0.11	<b>27%</b>	0.06 (0.02-0.46)
<b>Labetalol</b>	<b>53%</b>		0	NA	0	NA
amp	8%	1.46 (1.46-2.97)				
100mg tab	53%	0.20				

Price listed is per tab or amp in USD. Price charged was that charged to clients as reported by attending chemist or counter staff. \*Data from India on specific formulation of nifedipine not available. #Some pharmacies in Uganda and Mexico had more than one formulation of nifedipine thus total may add to >100%.

## CREATING DEMAND FOR HIGH-QUALITY ANTIHYPERTENSIVE MEDICINES

*“The policy on management of hypertensive in pregnancy does not match with the policy of the supply chain.”*

*-- Policymaker, Uganda*

Providers at healthcare facilities in Uganda and Mexico confirmed the need for guidance and updates on new treatment guidelines and appropriate products for use in HDP. As one policy maker in Uganda noted, “The policy on management of hypertensive in pregnancy does not match with the policy of the supply chain.” Some key informants in Uganda noted that providers cut tablets or adjusted dosing frequency or intervals in order to use available nifedipine formulations. In all three countries, providers reported some confusion about dosing for mild versus severe hypertension and requested greater clarification in national guidelines on dose escalation protocols with a single medicine or the use of a second medicine in the event of treatment failure with a single drug.

### ANTIHYPERTENSIVE MEDICINES

#### CHALLENGES

- The national EML alone may be insufficient to promote treatment of HDP
  - Labelled indications and/or formulation may require further clarification in practice guidelines.
  - Oral medicines may not be considered first line treatment for severe hypertension in pregnancy in national guidelines and/or not stocked at health facilities providing either basic or emergency obstetric services.
- Nifedipine was the most commonly available antihypertensive medicine in the three project countries though the product may not be an appropriate formulation for treatment of HDP (10mg immediate release) and/or current guidelines do not advise on use of alternative formulations
- Antihypertensive products available in all three project countries were of unknown quality

#### RECOMMENDATIONS

- Provide clarification and guidance in global and national EMLs and treatment guidelines on use of
  - oral medicines
  - different nifedipine formulations (immediate and modified release) and different dosages (e.g. 20mg tablets)
  - dose escalation protocols
  - treatment of mild vs. severe hypertension in pregnancy
- Assess the quality of marketed antihypertensive products given the low number of high quality verified products available globally

## 5. CONCLUSION

*“...I feel that hypertension is not getting [the] prominence it deserves in terms of supplies. Advocacy is missing or inadequate.”*

*--Technical Expert, Uganda*

Our landscape assessment of the availability of blood pressure devices and antihypertensive medicines for the treatment of hypertensive disorders of pregnancy found both supply and demand side challenges. For blood pressure devices, we found few national level quality assurance mechanisms to ensure the procurement of good quality devices and a lack of clarity around existing financing mechanisms for the replacement or upkeep of procured devices (whether for repair of existing machines or support of consumable items like batteries). Providers and key stakeholders in all three countries noted how the lack of this essential medical device resulted in a poor quality of care whether for the detection of elevated blood pressure in pregnancy or the monitoring of patients in need of ongoing treatment. The lack of blood pressure devices in turn influenced the use of antihypertensive medicines stocked for treatment of elevated blood pressure in pregnancy which, in turn, hampered procurement experts' ability to assess current use and forecast future need.

Current global guidelines for treatment of severe hypertension in pregnancy allow for use of different medicines depending upon the local context. While such flexibility is necessary given widespread variability in drug availability, it has also resulted in some confusion in implementation. Although nifedipine can be used for the treatment of general hypertension, methyldopa is only used in a relative small number of pregnancies with complications related to hypertension in pregnancy. As a result, we found nifedipine to be more widely available than methyldopa in these three countries. Additional research is needed to identify whether this issue is more widespread and whether additional guidance is necessary to aid country or sub-national procurement officers. In the short term, more global guidance is immediately required to clarify the use of different formulations of nifedipine for dose escalation protocols as such protocols may, in turn, impact procurement and forecasting needs for maternal health programs.

## Appendix 1. Document Review

### MEXICO

#### Law and Policy Documents

Ley General de Salud (Mexico Health's General Law).

Programa de Acción Específico 2013-2018 – Salud Materna y Perinatal (Mexico's Specific Action Program for 2013-2018).

NOM-007-SSA2-2016 Para la atención de la mujer durante el embarazo parto y puerperio y de la persona recién nacida (National Official Norm # NOM-007-2016: Care of Women During Pregnancy, Delivery & Post-partum, and Care of the Newly-born Person).

Guía de Práctica Clínica (GPC) # IMSS-058-08 (actualizada el 2017) para la Detección, Diagnóstico y Tratamiento de las Enfermedades Hipertensivas del Embarazo (Clinical Practice Guideline [GPC] (updated 2017): Screening, Diagnosis and Treatment of Hypertensive Disorders during Pregnancy).

GPC # IMSS-020-08 (actualizada en 2017) para la Prevención, Diagnóstico y Tratamiento de la Preeclampsia en el 2do. Y 3er. Nivel de Atención (GPC [updated 2017]: Prevention, Diagnosis and Treatment of Preeclampsia on the 2° and 3° Level of Care).

GPC # IMSS-436-11 (2011) para la Detección y Tratamiento Inicial de Emergencias Obstétricas (GPC: Screening and Initial Treatment of Obstetric Emergencies).

GPC COMEGO (2014): Intervenciones efectivas en la preeclampsia (COMEGO's GPC: Effective Interventions on Preeclampsia).

Lineamiento Técnico Nacional (2007): Prevención, Diagnóstico y Manejo de la Preeclampsia/Eclampsia (National Technical Guideline (2007): Prevention, Diagnosis and Management of Preeclampsia/Eclampsia).

CNEGSR - Lineamiento Técnico (2016): Triage obstétrico, Código Mater y Equipo de Respuesta Inmediata (CNEGSR's Technical Guideline: Obstetric Triage, Code MATER and Immediate Response Team).

GPC # SS-803-17 – Intervenciones de Enfermería para la atención de la emergencia obstétrica en los tres niveles de atención (GPC: Nursing Interventions for Management of Obstetric Emergencies at the Three Levels of Care).

GPC # SS-314-16 – Intervenciones de Enfermería para el control prenatal aplicada en el 1° nivel de atención (GPC: Nursing Interventions for Antenatal Care Applied to the First Level of Care).

GPC # IMSS-586-12 (actualizada en 2017)– Intervenciones de Enfermería para la prevención y atención de mujeres con Trastornos Hipertensivos en el Embarazo (GPC: Nursing Interventions for Prevention and Management of Women with Hypertensive Disorders during Pregnancy).

GPC # IMSS-586-12 (2012) – Intervenciones de Enfermería en la paciente con preeclampsia/eclampsia (GPC: Nursing Interventions on patients with Preeclampsia/Eclampsia).

DOF – Lista de Medicamentos y otros Insumos Esenciales para la Salud en México 2017 (Medicines & other Essential Supplies' Official List for Health in Mexico, 2017).

DOF – Segunda Actualización de la Edición 2017 del Cuadro Básico y Catálogo de Medicamentos, 2018 (Official 2nd Update of the 2017 Basic & Essential Medicines List, 2018).

Consejo de Salubridad General (CSG) – Cuadro Básico y Catálogo de Medicamentos 2017 (Mexico's General Health Council [CSG]: 2017 Basic & Essential Medicines List).

CSG – Cuadro Básico y Catálogo de Instrumental y Equipo Médico Tomos I, II y III 2017 (CSG: 2017 Basic & Essential Devices and Medical Equipment List, Vols. I, II & III).

CSG – Cuadro Básico y Catálogo de Auxiliares de Diagnóstico 2017 (CSG: 2017 Basic & Essential Screening Aids List).

CSG – Guía para la Evaluación de Insumos de Salud 2017 (CSG: 2017 Guideline to Evaluate Health Supplies).

Catálogo Universal de Servicios de Salud – CAUSES 2018 (Seguro Popular) (2018 Universal Catalog of Health Services).

IMSS – Cuadro Básico de Medicamentos 2018 (IMSS' 2018 Basic & Essential Medicines List).

## INDIA

### Law and Policy Documents

National Rural Health Mission, Maternal Health Division, Ministry of Health & Family Welfare, Government of India. 2014. Eclampsia Management.

National Rural Health Mission, Maternal Health Division, Ministry of Health & Family Welfare, Government of India. 2014. Pre-eclampsia Management.

National Rural Health Mission, Maternal Health Division, Ministry of Health & Family Welfare, Government of India. 2014. Prevention, Identification and Management of Pre-eclampsia and Eclampsia

Ministry of Health & Family Welfare, Government of India. Standard Treatment Guidelines Obstetrics & Gynaecology.

Maternal Health Division, Ministry of Health & Family Welfare, Government of India. 2014. National Guidelines for Calcium Supplementation During Pregnancy and Lactation

Ministry of Health & Family Welfare, Government of India. 2015. National List of Essential Medicines 2015

Maternal Health Division, Department of Family Welfare, Ministry of Health & Family Welfare Government of India. 2005. Guidelines for Pregnancy Care and Management of Common Obstetric Complications by Medical Officers.

Ministry of Health & Family Welfare, Government of India. Operational Guidelines: Free Drugs Service Initiative.

Ministry of Chemicals & Fertilizers Department of Pharmaceuticals. The review application of M/s Wockhardt Ltd dated 05/04/2016 under para 31 of DPCO against NPPA order No. S.O. 1254(E) dated 29/03/2016 for price fixation of Methyldopa Tablet 500mg.

National Health Policy (1983)

National Health Policy (2002)

Sample Registration Survey: Maternal Mortality Rate. (2001-03)

### Secondary Sources and White Papers

FOGSI Report on Hypertensive Disorders Of Pregnancy. 2014.

FOGSI Report of the National Eclampsia Registry. 2014.

Dr.Vandana Walvekar. Management of Complications of PIH: An Overview.

JHPIEGO. 2016. Dakshata- Government of India's strategic initiative for Quality Improvement in Labor Rooms. Fact Sheet

International Institute for Population Sciences (IIPS) and ICF. 2018. National Family Health Survey (NFHS-4), India, 2015-16: Maharashtra. Mumbai: IIPS. International

Institute for Population Sciences (IIPS), 2014.

District Level Household and Facility Survey (DLHS-4), 2012-13: India. Maharashtra: Mumbai: IIPS.National Health Systems Resource Centre. Data Management and Analysis: HMIS 2011-12.

Kotwani A. Where are we now: assessing the price, availability and affordability of essential medicines in Delhi as India plans free medicine for all. BMC Health Serv Res. 2013 Jul 25;13:285.

PubMed PMID: 23885985; PubMed Central PMCID: PMC3733775.

Leena Alfred, Shobha Rani R. H., Surjith K. Sharma, Jai Prakash S. Vastrad, Mahvash Iram. 2014. Antihypertensive Drugs used during Pregnancy: an Evaluation. *Journal of Pharmaceutical Research & Clinical Practice*. April-June 2014; 4(2):33-40 ISSN: 2231-4237

Millard C, Kadam AB, Mahajan R, Pollock AM, Brhlikova P. Availability of brands of six essential medicines in 124 pharmacies in Maharashtra. J Glob Health. 2018 Jun;8(1):010402.

Ramadurg et al. 2016. Community health worker knowledge and management of pre-eclampsia in rural Karnataka State, India. *Reproductive Health* 2016, 13(Suppl 2):113.

# UGANDA

## Law and Policy Documents

Uganda Vision 2040  
The Second National Development Plan 2015/16 – 2019/20 (NDPII)  
The Second National Health Policy (2010/11–2019/20)  
The National Health Sector Development Plan (2015/16 – 2019/20)  
Uganda National Medicines Policy 2015  
Essential Drugs List of Uganda  
National Pharmaceutical Sector Strategic Plan III 2015–2020  
National Drug Register of Uganda Human Medicines August 2019  
National Policy Guidelines and Service Standards for Maternal and Child Health  
Ministry of Health. Primary Health Care Grant Guidelines. FY 2016–2017.  
National Medical Equipment Policy. 4<sup>th</sup> Edition. 2009

## Secondary Sources and White Papers

Armstrong-Hough M, Kishore SP, Byakika S, Mutungi G, Nunez-Smith M, Schwartz JI. Disparities in availability of essential medicines to treat non-communicable diseases in Uganda: A Poisson analysis using the Service Availability and Readiness Assessment. *PloS One*. 2018 Feb 8;13(2):e0192332.

Chowfla A, Chitashvili T, Namajji C, Hermida J, Karamagi E, Holschneider S. 2018. Improving preeclampsia and eclampsia care. Tested changes and guidance from East Central Uganda. Published by USAID Applying Science to Strengthen and Improve Systems (ASSIST) Project. Chevy Chase, MD: University Research Co., LLC (URC).

Gutierrez R, Teshome S, Neilson M. 2018. Uganda's Health Care Quality Improvement Journey. Technical Report. Published by the USAID ASSIST Project. Chevy Chase, MD: University Research Co., LLC (URC).

Kibirige D, Atuhe D, Kampiire L, Kiggundu DS, Donggo P, Nabbaale J, Mwebaze RM, Kalyesubula R, Lumu W. Access to medicines and diagnostic tests integral in the management of diabetes mellitus and cardiovascular diseases in Uganda: insights from the ACCODAD study. *Int J Equity Health*. 2017 Aug 24;16(1):154.

Matovu, Brian. Regulation and Standards of Medical Devices in Uganda. Conference paper. November 2018

Musinguzi G, Bastiaens H, Wanyenze RK, Mukose A, Van Geertruyden JP, Nuwaha F. Capacity of Health Facilities to Manage Hypertension in Mukono and Buikwe Districts in Uganda: Challenges and Recommendations. *PloS One*. 2015 Nov 11;10(11):e0142312.

Ministry of Health (MOH)[Uganda] and Macro International Inc. 2008. Uganda Service Provision Assessment Survey 2007. Kampala, Uganda: Ministry of Health and Macro International Inc.

Nakimuli A, Nakubulwa S, Kakaire O, Osinde MO, Mbalinda SN, Kakande N, Nabirye RC, Kaye DK. The burden of maternal morbidity and mortality attributable to hypertensive disorders in pregnancy: a prospective cohort study from Uganda. *BMC Pregnancy Childbirth*. 2016 Aug 4;16:205.

Rawlins B, Plotkin M, Rakotovo JP, Getachew A, Vaz M, Ricca J, Lynam P, Kagema F, Gomez P. Screening and management of pre-eclampsia and eclampsia in antenatal and labor and delivery services: findings from cross-sectional observation studies in six sub-Saharan African countries. *BMC Pregnancy Childbirth*. 2018 Aug 23;18(1):346.

Rogers HE, Akiteng AR, Mutungi G, Ettinger AS, Schwartz JI. Capacity of Ugandan public sector health facilities to prevent and control non-communicable diseases: an assessment based upon WHO-PEN standards. *BMC Health Serv Res*. 2018 Aug 6;18(1):606.

Rugera, S. P., R. McNerney, et al. (2014). "Regulation of medical diagnostics and medical devices in the East African community partner states." *BMC health services research* 14(1).

Uganda Bureau of Statistics (UBOS) and ICF. 2018. Uganda Demographic and Health Survey 2016. Kampala, Uganda and Rockville, Maryland, USA: UBOS and ICF.



## INTERNATIONAL GUIDELINES AND POLICY DOCUMENTS

World Health Organization. WHO recommendations on antenatal care for a positive pregnancy experience. 2016. ISBN 978 92 4 154991 2.

World Health Organization. WHO recommendations on postnatal care of the mother and newborn. 2013.

World Health Organization. Managing complications in pregnancy and childbirth: a guide for midwives and doctors – 2nd ed. 2017.

World Health Organization. WHO recommendations: Drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

World Health Organization. USER GUIDE: WHO technical specification for medical devices Version 1.1 , 2014.

World Health Organization. Interagency list of priority medical devices for essential interventions for reproductive, maternal, newborn and child health, 2016.

World Health Organization. Affordable technology : blood pressure measuring devices for low resource settings. 2005.

ACOG Committee Opinion No. 767 Summary: Emergent Therapy for Acute-Onset, Severe Hypertension During Pregnancy and the Postpartum Period. *Obstet Gynecol.* 2019 Feb;133(2):409-412.

Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, Hall DR, Warren CE, Adoyi G, Ishaku S; International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens.* 2018 Jul;13:291-310.

USAID/OFDA Proposal Guidelines Pharmaceutical & Medical Commodity Guidance, April 2018.

WHO/HAI. Measuring medicine prices, availability, affordability and price components. 2<sup>nd</sup> Edition. 2008.

## SECONDARY SOURCES AND WHITE PAPERS

Bazzano AN, Green E, Madison A, et al. Assessment of the quality and content of national and international guidelines on hypertensive disorders of pregnancy using the AGREE II instrument. *BMJ Open* 2016;6:e009189.

Bello NA, Woolley JJ, Cleary KL, Falzon L, Alpert BS, Oparil S, Cutter G, Wapner R, Muntner P, Tita AT, Shimbo D. Accuracy of Blood Pressure Measurement Devices in Pregnancy: A Systematic Review of Validation Studies. *Hypertension.* 2018 Feb;71(2):326-335.

Bryan, Jenny. Nifedipine: from the treatment of angina to the treatment of hypertension. *The Pharmaceutical Journal*, Vol. 284, p507.

Cairns AE, Pealing L, Duffy JMN, et al. Postpartum management of hypertensive disorders of pregnancy: a systematic review. *BMJ Open* 2017;7:e018696.

Cameron A, Ewen M, Ross-Degnan D, Ball D, Laing R. Medicine prices, availability, and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet.* 2009 Jan 17;373(9659):240-9.

Cameron A, Roubos I, Ewen M, Mantel-Teeuwisse AK, Leufkens HG, Laing RO. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Health Organ.* 2011 Jun 1;89(6):412-21.

Cohen JB, Padwal RS, Gutkin M, Green BB, Bloch MJ, Germino FW, Sica DA, Viera AJ, Bluml BM, White WB, Taler SJ, Yarows S, Shimbo D, Townsend RR. History and Justification of a National Blood Pressure Measurement Validated Device Listing. *Hypertension*. 2019 Feb;73(2):258-264.

Droti B, O'Neill KP, Mathai M, et al. Poor availability of essential medicines for women and children threatens progress towards Sustainable Development Goal 3 in Africa. *BMJ Global Health* 2019;4:001306.

Gillon TER, Pels A, von Dadelszen P, MacDonell K, Magee LA (2014) Hypertensive Disorders of Pregnancy: A Systematic Review of International Clinical Practice Guidelines. *PLoS ONE* 9(12): e113715.

Guidotti R and Jobson D. Detecting pre-eclampsia, a practical guide Using and maintaining blood pressure equipment. WHO 2005.

Lalani S, et al. Pharmacotherapy for preeclampsia in low and middle income countries: an analysis of essential medicines lists. *J Obstet Gynaecol Can*. 2013. Mar;35(3):215-223.

MSH (Management Sciences for Health). 2016. *International Medical Products Price Guide*, 2015 (Edition).

Magee, L et al. The FIGO Textbook of Pregnancy Hypertension: An evidence-based guide to monitoring, prevention and management.

Medley N, Poljak B, Mammarella S, Alfirevic Z. Clinical guidelines for prevention and management of preterm birth: a systematic review. *BJOG* 2018;125:1361-1369.

Nathan HL, Duhig K, Hezelgrave NL, Chappell LC, Shennan AH. Blood pressure measurement in pregnancy. *The Obstetrician & Gynaecologist* 2015;17:91-8.

Nathan HL, Vousden N, Lawley E, de Greeff A, Hezelgrave NL, Sloan N, Tanna N, Goudar SS, Gidiri MF, Sandall J, Chappell LC, Shennan AH. Development and evaluation of a novel Vital Signs Alert device for use in pregnancy in low-resource settings. *BMJ Innov*. 2018 Oct;4(4):192-198.

Nathan HL, Duhig K, Vousden N, Lawley E, Seed PT, Sandall J, Bellad MB, Brown AC, Chappell LC, Goudar SS, Gidiri MF, Shennan AH; CRADLE-3 Trial Collaboration Group. Evaluation of a novel device for the management of high blood pressure and shock in pregnancy in low-resource settings: study protocol for a stepped-wedge cluster-randomised controlled trial (CRADLE-3 trial). *Trials*. 2018 Mar 27;19(1):206.

Nathan HL, Boone H, Munguambe K, Sevene E, Akeju D, Adetoro OO, Charanthimath U, Bellad MB, de Greeff A, Anthony J, Hall DR, Steyn W, Vidler M, von Dadelszen P, Chappell LC, Sandall J, Shennan AH; CLIP Working Group. The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *Reprod Health*. 2018 Jan 5;15(1):5.

PATH. Antihypertensive drugs for the management and treatment of hypertensive disorders of pregnancy Technology Opportunity Assessment. March 2014.

Raichle CJ, Eckstein J, Lapaire O, Leonardi L, Brasier N, Vischer AS, Burkard T. Performance of a Blood Pressure Smartphone App in Pregnant Women: The iPARR Trial (iPhone App Compared With Standard RR Measurement). *Hypertension*. 2018 Jun;71(6):1164-1169.

Sachiko Ozawa, et al. Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries A Systematic Review and Meta-analysis. *JAMA Network Open*. 2018;1(4):e181662.

Shimek, J, ed. Replacement of mercury thermometers and sphygmomanometers in health care: technical guidance. World Health Organization. 2011.

Stergiou GS, O'Brien E, Myers M, Palatini P, Parati G, Kollias A, Birmpas D, Kyriakoulis K, Bountzona I, Stambolliu E, Anagnostopoulos I, Karpettas N, Menti A; STRIDE BP Scientific Advisory Board. STRIDE BP international initiative for accurate blood pressure measurement: Systematic review of published validation studies of blood pressure measuring devices. *J Clin Hypertens (Greenwich)*. 2019 Nov;21(11):1616-1622.

Stergiou GS, Alpert B, Mieke S, Asmar R, Atkins N, Eckert S, Frick G, Friedman B, GraBl T, Ichikawa T, Ioannidis JP, Lacy P, McManus R, Murray A, Myers M, Palatini P, Parati G, Quinn D, Sarkis J, Shennan A, Usuda T, Wang J, Wu CO, O'Brien E. A Universal Standard for the Validation of Blood Pressure Measuring Devices: Association for the Advancement of Medical Instrumentation/European Society of Hypertension/International Organization for Standardization (AAMI/ESH/ISO) Collaboration Statement. *Hypertension*. 2018 Mar;71(3):368-374.

Twagirumukiza M, Annemans L, Kips JG, Bienvenu E, Van Bortel LM. Prices of antihypertensive medicines in sub-Saharan Africa and alignment to WHO's model list of essential medicines. *Trop Med Int Health*. 2010 Mar;15(3):350-61.

Twagirumukiza M, Cosijns A, Pringels E, Remon JP, Vervaet C, Van Bortel L. Influence of tropical climate conditions on the quality of antihypertensive drugs from Rwandan pharmacies. *Am J Trop Med Hyg*. 2009 Nov;81(5):776-81.

van Mourik MS, Cameron A, Ewen M, Laing RO. Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data. *BMC Cardiovasc Disord*. 2010 Jun 9;10:25.

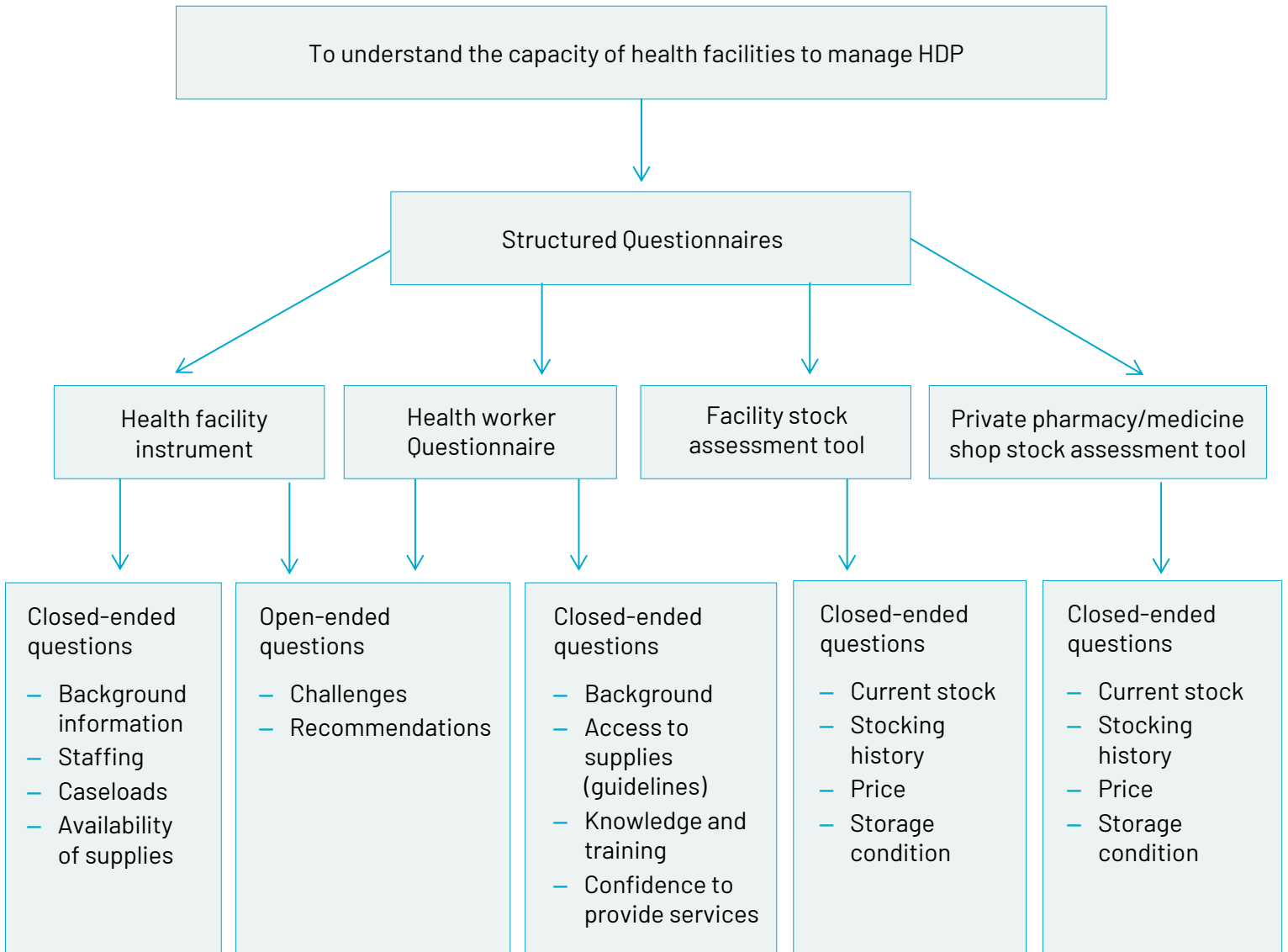
## Appendix 2. List of stakeholders consulted

Country	Position	Organization	Role
MEXICO	Maternal & Antenatal Health Under Director	Centro Nacional de Equidad de Género y Salud Reproductiva (CNEGSR)	Service provision
	Specialist Medical Advisor Norms & Guidelines Developer	Centro Nacional de Equidad de Género y Salud Reproductiva (CNEGSR)	Service provision, technical assistance
	Maternal Health Coordinator	Secretaría de Salud de la Ciudad de México (SEDESA)	Service provision
	Reproductive Health Coordinator	Secretaría de Salud de la Ciudad de México (SEDESA)	Service provision
	Secretary	Comité Estatal de Mortalidad Materna y Perinatal de la Ciudad de México	Service provision, technical assistance, research
	Medical Director	Instituto Nacional de Perinatología (INPer)	Service provision, research, procurement
	Head of Maternal Health	Instituto de Salud del Estado de México (ISEM)	Service provision
	Medical Director Maternal Health Program	Secretaría de Salud del Estado de Hidalgo	Service provision, procurement
	Teacher Researcher in Nursing Services	Instituto Politécnico Nacional (IPN) – Escuela Superior de Enfermería y Obstetricia (ESE0)	Service provision, technical assistance
	Technical Secretary	Comité Promotor por una Maternidad Segura (CPMS)	Service provision, technical assistance
	Chief of Department	Secretaría de Salud de la Ciudad de México (SEDESA)	Service provision, technical assistance
Head of Maternal Health	Secretaría de Salud del Estado de Chiapas (Jurisdicción Sanitaria II)	Service provision, technical, procurement	

Country	Position	Organization	Role
UGANDA	Commissioner	Reproductive Health Division, Ministry of Health	Policy
	Professor	Makerere University	Research
	Assistant Commissioner	Reproductive Health and Infant Health, Ministry of Health	Policy and technical assistance
	Reproductive Health Advisor	World Bank	Technical Assistance
	Gynaecologist	Ministry of Health	Service provision
	Clinical Director	National Referral Hospital	Service Provision, technical assistance
	Chairperson, National Advisory Committee on Medical Equipment	Ministry of Health	Technical assistance, procurement
	Maternal Health Advisor	Uganda Catholic Medical Bureau	Technical assistance
	Professor	Uganda Martyrs University	Service provision and research
	Program Officer	JHPIEGO	Technical assistance
	Program Officer	UNFPA	Procurement, technical assistance
	President	Association of Obstetricians and Gynecologists Uganda (AOGU)	Technical assistance
	Principle Advocacy and Customer Care	National Medical Stores	Procurement
Engineer	Ministry of Health	Procurement	

Country	Position	Organization	Role
INDIA	Deputy Commissioner, Maternal Health	Ministry of Health & Family Welfare	Service provision, procurement
	Nodal person	National Health Systems Resource Centre	Service provision, procurement
	Program Director	JHPIEGO	Implementation
	Senior Technical Advisor	JHPIEGO	Technical assistance
	Professor, Physiology	Jawaharlal Nehru Medical College	Research, technical expert, procurement
	Professor, Community Medicine	Jawaharlal Nehru Medical College	Research, technical expert
	Gynecologist, Ex-President	Federation of Obstetricians and Gynecologists of India (FOGSI)	Service provision
	Gynaecologist	Indian Medical Association (IMA)	Technical assistance, service provision
	FOGSI member, In-charge national eclampsia registry	FOGSI	Research, service provision
	Gynaecologist, member FOGSI	FOGSI	Service provision
Gynaecologist, member FOGSI	FOGSI	Service provision	

### Appendix 3. Facility Survey Study Design



## 6. CITATIONS

- 
- <sup>1</sup> WHO recommendations on antenatal care for a positive pregnancy experience. (WHO: 2016).
- <sup>2</sup> *Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors* – 2nd ed (WHO, 2017).
- <sup>3</sup> WHO recommendations on postnatal care of the mother and newborn (WHO: 2013)
- <sup>4</sup> Shimek, WHO 2005
- <sup>5</sup> <https://www.iso.org/standard/73339.html>
- <sup>6</sup> Stergiou, 2019
- <sup>7</sup> <https://www.ama-assn.org/delivering-care/hypertension/ama-aha-developing-list-validated-bp-monitors>  
Cohen JB, Padwal RS, Gutkin M, Green BB, Bloch MJ, Germino FW, Sica DA, Viera, AJ, Bluml BM, White WB, Taler SJ, Yarows S, Shimbo D, Townsend RR. History and Justification of a National Blood Pressure Measurement Validated Device Listing. *Hypertension*. 2019 Feb;73(2):258-264.
- <sup>8</sup> Bello NA, Woolley JJ, Cleary KL, Falzon L, Alpert BS, Oparil S, Cutter G, Wapner R, Muntner P, Tita AT, Shimbo D. Accuracy of Blood Pressure Measurement Devices in Pregnancy: A Systematic Review of Validation Studies. *Hypertension*. 2018 Feb;71(2):326-335.
- <sup>9</sup> Nathan HL, Vousden N, Lawley E, de Greeff A, Hezelgrave NL, Sloan N, Tanna N, Goudar SS, Gidiri MF, Sandall J, Chappell LC, Shennan AH. Development and evaluation of a novel Vital Signs Alert device for use in pregnancy in low-resource settings. *BMJ Innov*. 2018 Oct;4(4):192-198.
- <sup>10</sup> Nathan HL, Duhig K, Vousden N, Lawley E, Seed PT, Sandall J, Bellad MB, Brown AC, Chappell LC, Goudar SS, Gidiri MF, Shennan AH; CRADLE-3 Trial Collaboration Group. Evaluation of a novel device for the management of high blood pressure and shock in pregnancy in low-resource settings: study protocol for a stepped-wedge cluster-randomised controlled trial (CRADLE-3 trial). *Trials*. 2018 Mar 27;19(1):206.
- <sup>11</sup> Nathan HL, Boene H, Mungambe K, Sevene E, Akeju D, Adetoro OO, Charanthimath U, Bellad MB, de Greeff A, Anthony J, Hall DR, Steyn W, Vidler M, von Dadelszen P, Chappell LC, Sandall J, Shennan AH; CLIP Working Group. The CRADLE vital signs alert: qualitative evaluation of a novel device designed for use in pregnancy by healthcare workers in low-resource settings. *Reprod Health*. 2018 Jan 5;15(1):5.
- <sup>12</sup> <http://ish-world.com/news/a/The-CRADLE-Vital-Signs-Alert/>
- <sup>13</sup> <https://www.who.int/reproductivehealth/innovative-blood-pressure-measurement/en/>
- <sup>14</sup> <https://www.nda.or.ug/medical-devices-guidelines/>
- <sup>15</sup> [https://www.icmr.nic.in/sites/default/files/press\\_release\\_files/IHCL\\_op.pdf](https://www.icmr.nic.in/sites/default/files/press_release_files/IHCL_op.pdf)
- <sup>16</sup> *Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors* – 2nd ed (WHO, 2017).
- <sup>17</sup> WHO recommendations: drug treatment for severe hypertension in pregnancy. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
- <sup>18</sup> Lalani S, et al. Pharmacotherapy for preeclampsia in low and middle income countries: an analysis of essential medicines lists. *J Obstet Gynaecol Can*. 2013 Mar;35(3):215-223.
- <sup>19</sup> [https://apps.who.int/iris/bitstream/handle/10665/75154/WHO\\_EMP\\_MAR\\_2012.1\\_eng.pdf;jsessionid=F18C322078645D749E72EDAB5E7266DF?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/75154/WHO_EMP_MAR_2012.1_eng.pdf;jsessionid=F18C322078645D749E72EDAB5E7266DF?sequence=1)
- <sup>20</sup> [https://www.usaid.gov/sites/default/files/documents/1866/USAID-FDA\\_Pharmaceutical\\_Guidance\\_April\\_2018.pdf](https://www.usaid.gov/sites/default/files/documents/1866/USAID-FDA_Pharmaceutical_Guidance_April_2018.pdf)
- <sup>21</sup> Easterling T, Mundle S, Bracken H, Parvekar S, Mool S, Magee LA, von Dadelszen P, Shochet T, Winikoff B. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. *Lancet*. 2019 Aug 1. pii: S0140-6736(19)31282-6.
- <sup>22</sup> <https://supply.unicef.org/>
- <sup>23</sup> <https://www.unfpaprocedurement.org/products>
- <sup>24</sup> <https://www.chemistanddruggist.co.uk/news/local-nifedipine-shortages-continue-after-adalat-discontinuation>
- <sup>25</sup> [/economictimes.indiatimes.com/articleshow/63341092.cms?from=mdr&utm\\_source=contentofinterest&utm\\_medium=text&utm\\_campaign=cppst](https://economictimes.indiatimes.com/articleshow/63341092.cms?from=mdr&utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst)
- <sup>26</sup> Sachiko Ozawa, et al. Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries A Systematic Review and Meta-analysis. *JAMA Network Open*. 2018;1(4):e181662.