

Discussion Session: Availability of Pre-eclampsia/Eclampsia Medicines and the Role of Screening Tests and Devices

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Sessions Outline

- Introduction and Discussion: Deborah Armbruster (USAID)/Seun Aladesanmi (CHAI) – what are the existing diagnostics/interventions/innovations to address pre-eclampsia/eclampsia and what are the challenges getting them to scale?
- Ghana Anti-Hypertensive Commodities Analysis: (Siobhan Perkins – GHSC-PSM)
- PE/E Diagnostics Innovation - Evaluating the Effectiveness of Triage PIGF Assay in Mozambique: Seun Aladesanmi/Beatriz Manriquez Rocha (CHAI)
- New PE/E Research and Tools: Late breaking news – potential groundbreaking progress towards identifying the root cause and potential therapy for PE/E – Debbie Armbruster (USAID)

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what are the existing interventions and innovations to address pre-eclampsia/eclampsia

Waiting for responses ...



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what are the challenges and barriers getting them to scale

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Background - Pre-eclampsia/Eclampsia (PE/E)

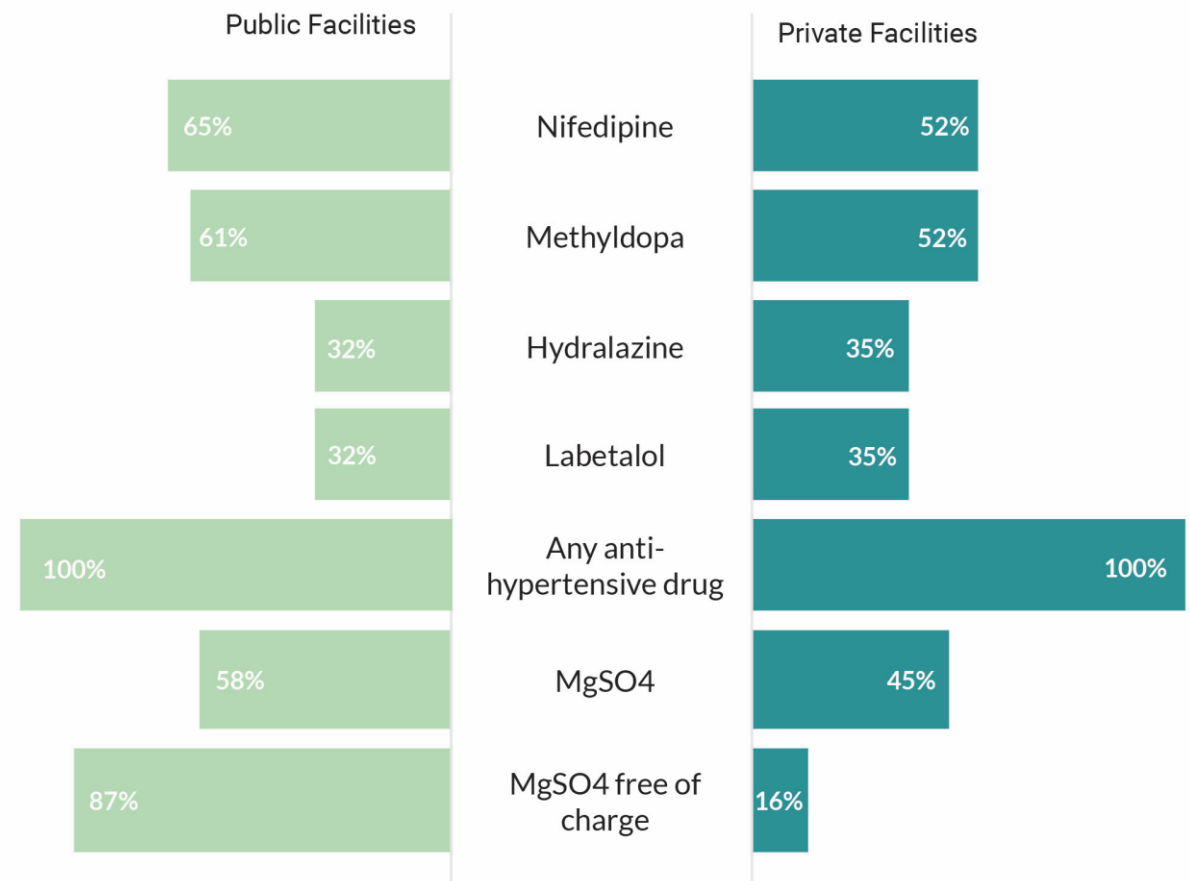
- Pre-eclampsia (PE) represents a substantial contributor to maternal and neonatal morbidity and mortality globally. The diagnosis of pre-eclampsia largely hinges on early detection of hypertension and proteinuria.
- In low-resource settings, diagnosis is challenging due to late ANC booking (± 22 weeks gestation), low >4 ANC visits coverage, and lack of functional blood pressure monitors and routine monitoring.
- Few interventions to address PE/E have been scaled up in LMICs.



Theme 1: Essential Drug Availability*

- HDP drug availability is less than optimal in both the public and private sector.
- While each country reported at least one WHO-recommended anti-hypertensive is on the EML and available at facilities, countries reported varied rates of regularly available anti-hypertensives.
- In addition, MgSO₄, the first-line anti-convulsant recommended for all women with severe PE/E, is only available regularly by 58% of countries in the public sector and 45% of countries in the private facilities.

Regular availability of HDP drugs in public and private sectors 2022



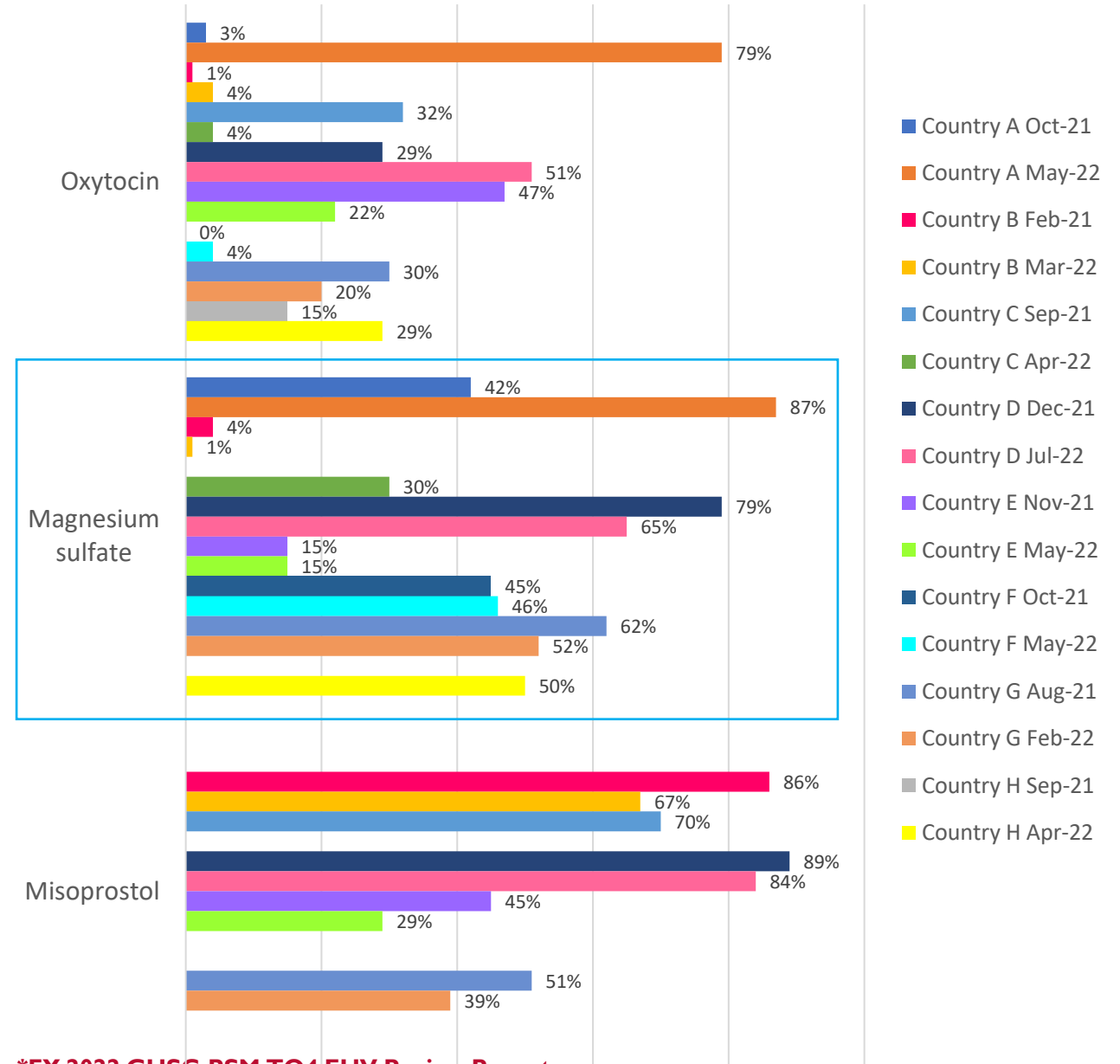
*2022 MCGL/MPHD Global Survey on Nat. Programs for Prevention and Management of PPH and Hypertensive Disorders of Pregnancy – IMNHC conference presentation

Regularly available is defined as > 80% of the time

PROVIDING COMMODITY VISIBILITY GHSC-PSM TO4 EUV SUMMARY*

- Maternal, newborn, and child health (MNCH) data and analytics within national LMISs are not always adequate to identify and resolve supply chain issues.
- The USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project uses the end-use verification (EUV) survey to increase the availability of MNCH commodity data.
- The survey helps supply chain staff collect data on commodity availability, storage conditions, and factors that affect commodity availability at service delivery points (SDPs).
- EUV data collection is also an opportunity for GHSC-PSM country teams to provide on-site capacity building for SDP staff and Ministries of Health (MoHs), gather supplemental qualitative data on reasons for stockouts, and cross-check LMIS data accuracy on stock availability trends.

% Stockout, Day of Visit, Health Facility Level
Maternal Commodities



HDP Assessment: Ghana

Assessment on hypertensive disorders in pregnancy (HDP) medicines:

- Availability of HDP products in the public health sector
- Care provider behaviors, practices, and preferences
- Case management and prescriber behavior

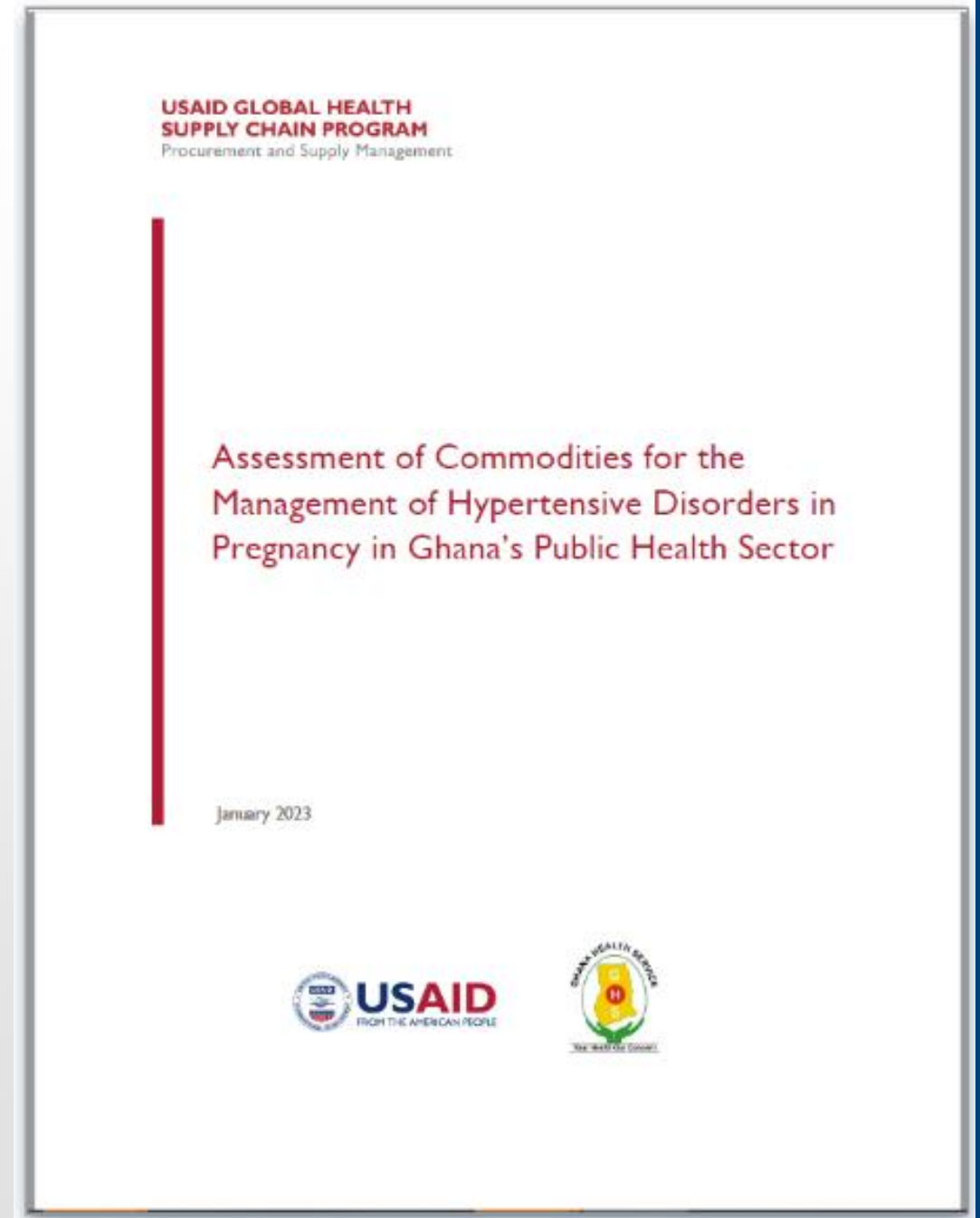
Quantitative component:

- 12 products
- 135 health facilities across 6 regions* in Ghana
 - 45 CHPS compounds
 - 60 health centers
 - 5 polyclinics
 - 25 hospitals

Qualitative component:

- Regional Medical Stores (RMS) administrators
- Chief Pharmacists at Regional Health Administration offices.

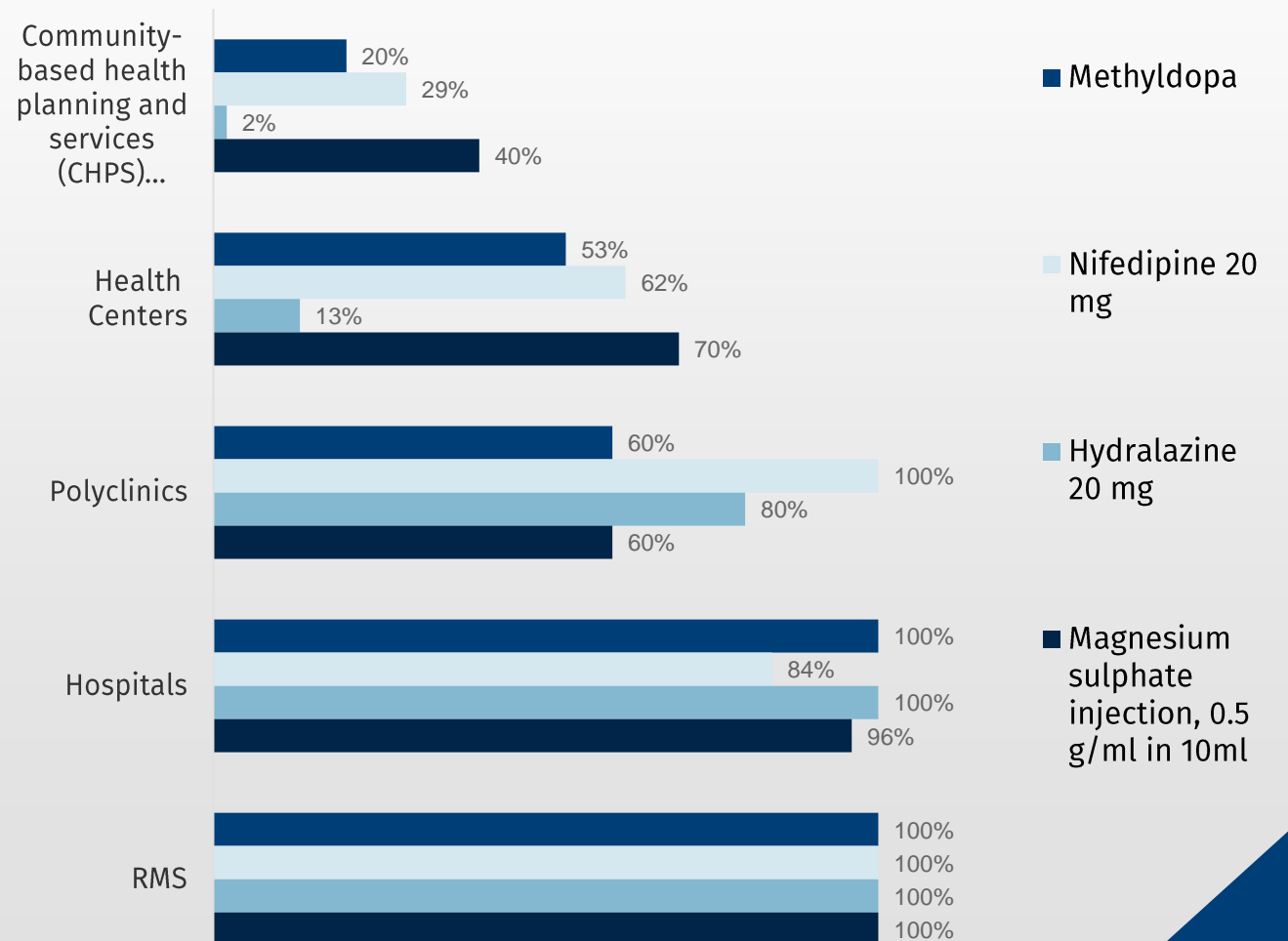
*Ashanti, Eastern, Greater Accra, Upper East, Northern/North East, Upper West



Select findings: management, availability and supply

- 70% of clients obtain their HDP medication from health facilities within the public sector
- Nifedipine is the preferred anti-hypertensive medication for pregnant women, followed by methyldopa
- CHPS & health centers cite “above level of care” as reason for non-management of product
- 50-70% of health facilities source products from RMS, per policy
- Main reasons for stockouts: non-availability at the supply point, product rationing and inadequate funds
 - Expiries of magnesium sulfate and calcium gluc due to low demand
- 44% of products were not registered with Ghana FDA

Management of HDP Products in Health Facilities



Next steps: HDP assessment

- Continued support to MOH, GHS, NHIS & and national health supply chain managers on recommendations
- The assessment tool will be refactored to enable its use in additional contexts
- Additional assessments will be conducted in 2-3 countries
- Post-marketing surveillance with Monash University in select countries



Photo credit: GHSC-PSM Ghana

Overview – Evaluating the Effectiveness of Triage PIGF Assay

- Triage Assay is a highly predictive biomarker for poor placental implantation and related complications, primarily pre-eclampsia.
- The PIGF test stratifies risk for pre-eclampsia and helps identify high-risk patients for adverse pregnancy outcomes, such as preterm deliveries.
- The data collected aids healthcare providers in determining whether to maintain current monitoring, refer the patient to a specialist, or take immediate action in managing the pregnancy.



The PIGF test contributes valuable insights, but its results should be evaluated in conjunction with other clinical factors before making a decision to intervene in the pregnancy.

Joint Initiative on Pre-Eclampsia: A Collaboration between CHAI, the Mozambique MOH and International Specialists

Outcomes from Initial PlGF Testing and Operational Research in Resource-Limited Settings:

- Mozambique is among the first countries to pilot the PlGF Triage Assay for pre-eclampsia.
- Three studies in Mozambique leverage the Placental Growth Factor (PlGF) test to enhance PE diagnostic procedures and management strategies.

- CHAI Mozambique, in partnership with the Ministry of Health (MoH) and an international advisory committee specializing in PE, spearheaded device evaluation and field operational studies.
- Objective to assess the correlation of low PlGF levels with metrics including confirmed PE diagnosis, elevated blood pressure, escalation of care, early gestational age delivery, delivery timing, preterm birth, cesarean delivery, low birth weight, perinatal loss, and stillbirth.

CHAI, and the Mozambique MoH, conducted two initial studies between 2014 and 2016 in Maputo city.

1

Diagnostic Performance of Placental Growth Factor in Women with Suspected Preeclampsia Attending Antenatal Facilities in Maputo, Mozambique.

- **Objective:** To assess the efficacy of maternal plasma-free PLGF in identifying women at risk for complicated preeclampsia in antenatal care settings in Maputo.
- **Key Findings:** Data indicated that women with PLGF levels below 100pg/ml faced significantly shorter time intervals to childbirth. This emphasizes the necessity for swift diagnosis and expedited referral to advanced care facilities.

2

Early diagnosis of preeclampsia using placental growth factor: an operational pilot study in Maputo, Mozambique.

- **Objective:** To understand the relationship between PLGF levels and stillbirth rates among high-risk preeclampsia cases in Maputo.
- **Key Findings:** The study found a 23% risk of stillbirth among women in the high-risk category for preeclampsia (PLGF <100pg/ml). For those in the very high-risk category (PLGF <50pg/ml), the stillbirth rate escalated to 32.6%.

Implications: These findings underscore the need for risk stratification in preeclampsia cases. They advocate for timely referrals to specialized care and the incorporation of the PLGF biomarker into clinical decision-making protocols for managing pathological pregnancies.

Initial Studies Indicate PlGF Testing Elevates Detection and Management of High-Risk Pre-Eclampsia

- In response to initial study findings, CHAI partnered with the MoH and obstetric experts to enhance the management of high-risk pregnancies.
- An operational implementation strategy has been rolled out across 44 referral health facilities in four provinces.
- Expansion to a fifth province successfully achieved in 2023.
- The program focuses on three key objectives:
 1. Early detection of Pre-Eclampsia (PE)
 2. Prompt referral and effective case management
 3. Reduction in Eclampsia incidences

Evaluating the Impact of PlGF Test Clinical Algorithm in Inhambane Province: A Collaborative Study by CHAI and MOH

3

In August 2019, the MoH and CHAI initiated an operational study:

- Hospital Provincial de Inhambane and Hospital Rural de Chicuque in Inhambane Province.
- Results are currently being prepared for international publication.
- Additional cost-effectiveness/cost-benefits analysis underway



Bundled case management strategy encompasses:

- 1. Initial screening and diagnostic tests** for women at local primary health centers.
2. Comprehensive **patient education for at-risk** women, including next steps and family communication, **prior to transfer to advanced care settings.**
- 3. Targeted referral of high-risk** women, identified via PlGF testing, to tertiary healthcare facilities.
4. Implementation of **structured clinical algorithm, providing clinicians with clear guidelines** for individualized case evaluation and informed decision-making on care and birthing options.

- **Study achieved a significant 19% reduction in eclampsia cases, particularly among high-risk gestational ages (20 to 32+6 weeks), demonstrating its positive impact on maternal morbidity.**
- **While study showed marked improvements in maternal outcomes for those with PE, evidence on neonatal morbidity impact remains limited.**

Confidential- Results yet to be published

Lifesaving Potential and Barriers of Innovative Screening in Resource-Limited Settings

Opportunities

- **Innovative Screening Bundle:** Life-saving potential exists through a comprehensive care bundle for PE, including BP monitors, Triage Metre, Referrals, Magnesium Sulphate, Anti-Hypertensives, Low Dose Aspirin, and HCW mentoring.
- **Scalability:** Approach has proven efficacy in low-resource settings and offers national scaling potential in Mozambique for uniform PlGF test access.
- **Regional Expansion:** Leverage findings and lessons from Mozambique for pilot programs in other African countries.
- **Cost-Reduction Strategies:** Market-shaping efforts present an opportunity to lower device and cartridge costs, with suppliers willing to offer devices for free.
- **Future Tests/Prophylaxis:** Upcoming tests like **Perkin Elmer**, costing around £15, in the trial phase with market entry expected in 2-3 years and **blood test M-PREG®** and oral active pill, designed to prevent preeclampsia

Barriers

- **Cost Barriers:** High device costs (\$2,500) and cartridge costs (~\$23 per woman, even with a negotiated 5% discount) are a concern.
- **Funding Gaps:** General lack of funding in Maternal and Neonatal Health (MNH), especially for PE/E management.
- **Limited Resources:** Despite limited funding, CHAI Mozambique has successfully developed a proof of concept, updated guidelines, and executed multiple operational studies.

Hot of the Press –Cis P-tau-early etiological driver

- Etiologic drivers for PE remain elusive.
- Cis P-tau is early etiological driver and blood biomarker for pre-clinical Alzheimers and after vascular or traumatic brain injury and can be targeted by a stereo-specific antibody.
- Researchers found significant cis P-tau in the placenta and serum of PE patients and in primary human trophoblasts exposed to hypoxia or sera from PE pts.
- While further research is needed, current research has discovered an early disease driver, and offer an early biomarker and effective antibody treatment for PE

> Nat Commun. 2023 Sep 5;14(1):5414. doi: 10.1038/s41467-023-41144-6.

Cis P-tau is a central circulating and placental etiologic driver and therapeutic target of preeclampsia

Sukanta Jash¹, Sayani Banerjee¹, Shibin Cheng¹, Bin Wang², Chenxi Qiu², Asami Kondo², Jan Ernerudh^{3 4}, Xiao Zhen Zhou^{5 6 7 8}, Kun Ping Lu^{9 10 11}, Surendra Sharma^{12 13}

Affiliations + expand

PMID: 37669931 PMCID: PMC10480164 DOI: 10.1038/s41467-023-41144-6

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Abstract

Preeclampsia (PE) is the leading cause of maternal and fetal mortality globally and may trigger dementia later in life in mothers and their offspring. However, the etiological drivers remain elusive. Cis P-tau is an early etiological driver and blood biomarker in pre-clinical Alzheimer's and after vascular or traumatic brain injury, which can be targeted by stereo-specific antibody, with clinical trials ongoing. Here we find significant cis P-tau in the placenta and serum of PE patients, and in primary human trophoblasts exposed to hypoxia or sera from PE patients due to Pin1 inactivation. Depletion of cis P-tau from PE patient sera by the antibody prevents their ability to disrupt trophoblast invasion and endovascular activity and to cause the PE-like pathological and clinical features in pregnant humanized tau mice. Our studies uncover that cis P-tau is a central circulating etiological driver and its stereo-specific antibody is valuable for early PE diagnosis and treatment.

FDA Clearance of Investigational New Drug - siRNA Investigational Therapy for the Treatment of Preeclampsia

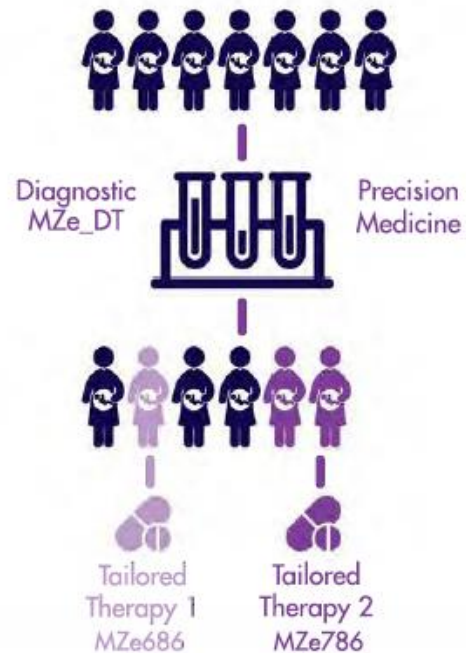
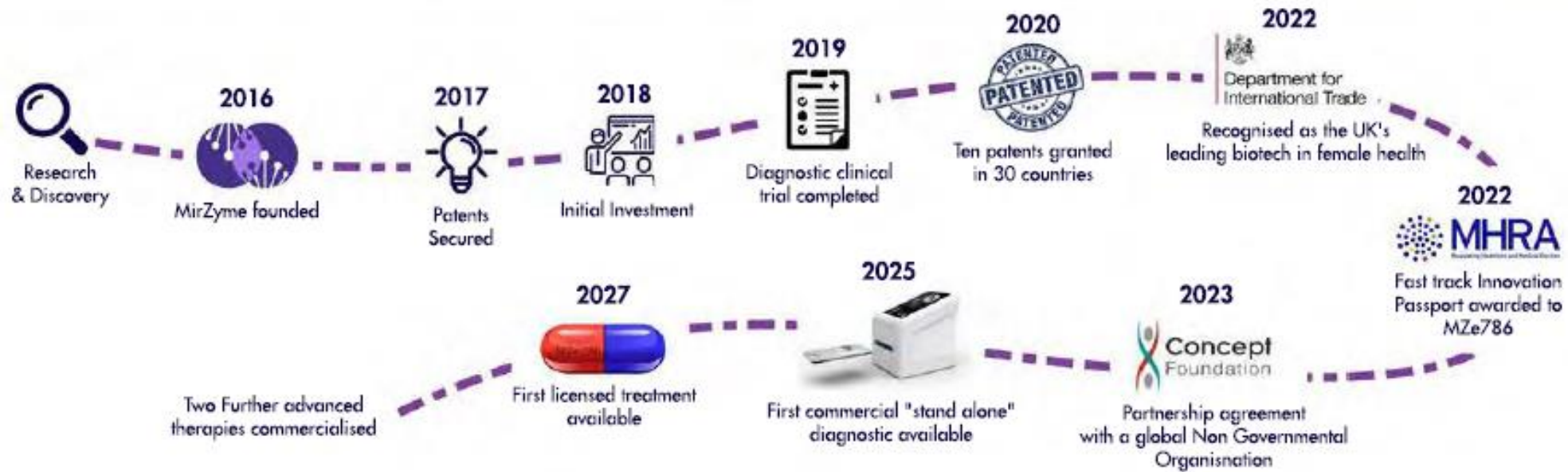
- FDA Clearance of Investigational New Drug
- siRNA Investigational Therapy for the Treatment of Preeclampsia
- CBP-4888 is a fixed-dose combination of 2 chemically synthesized, lipid-conjugated small interfering ribonucleic acid (siRNAs) duplex oligonucleotides (siRNA-2283 and siRNA-2519).
- The investigational therapy is designed to decrease the production of soluble fms-like tyrosine kinase-1 (sFLT1) mRNA isoforms in the placenta.

Comanche Biopharma Announces FDA Clearance of Investigational New Drug (IND) Application for CBP-4888, an siRNA Investigational Therapy for the Treatment of Preeclampsia

Published: Mar 30, 2023

CONCORD, Mass., March 30, 2023 /PRNewswire/ -- **Comanche Biopharma Corp.**, a biopharmaceutical company, today announced that the **U.S. Food and Drug Administration (FDA)** has cleared an investigational new drug (IND) application for Comanche's novel, siRNA therapy to treat preeclampsia. Preeclampsia is a prevalent hypertensive disorder of pregnancy for which there is no existing therapy that can modify disease progression.

"The FDA's clearance of CBP-4888 allows us to take another major step toward developing a treatment for preeclampsia," said Scott Johnson, M.D., Co-Founder and



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Blood test M-PREG[®] and oral active pill, designed to prevent/treat preeclampsia in the pipeline.

Questions and Discussions