Unitaid
SAVE LIVES FASTER

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Area for Intervention:
Improving risk detection and management of pre-eclampsia

Programmatic Priority: Women's and Children's Health
Improve access to better tools for safe pregnancy and birth for women and newborns

For Information ☐ **For Review and Advice** ☐ **For Decision** ☒

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1. Purpose and context of this document

In December 2020, Unitaid's Executive Board endorsed an Area for Intervention (AfI) on *New Tools for Reducing Maternal Mortality*, including efforts to better address post-partum haemorrhage (PPH) and pre-eclampsia (PE) in low-resource settings. This document provides an update on the PE landscape and potential opportunities for Unitaid, including the rationale for prioritization and a proposed way forward.

2. Introduction

Unitaid's Programmatic Priority on Women's and Children's Health: *Improve access to better tools for safe pregnancy and birth for women and newborns* is focused on catalyzing access to tools that prevent, diagnose, and treat the conditions that lead to significant maternal and newborn morbidity and mortality. Pre-eclampsia – a high blood pressure (hypertension) disorder that can occur during pregnancy – is one of biggest drivers of maternal mortality and a major risk factor for stillbirth and preterm birth, with the vast majority of poor outcomes occurring in low-and middle-income countries (LMICs). Unitaid's 2023-2027 Strategy identified pre-eclampsia as a high priority and highlighted the potential to accelerate adoption of new diagnostic tools through evidence generation, market shaping, and demand generation activities. These tools were also included in Unitaid's 30x30 mapping of 30 key innovations for introduction by 2030.

Following an updated analysis, the Secretariat proposes positioning prioritized opportunities to better address PE in the baseline funding scenario of the investment plan for 2025. Further opportunities related to PE are positioned in the upside scenario and could be supported if additional funds were to become available.

3. Public health challenge and key access issues

Every day, over 800 women die due to complications in pregnancy and childbirth. Nearly all of these deaths (94%) occur in LMICs. From 2000 to 2015, the global annual rate of maternal mortality reduction was 2.7%, but progress has since stalled and efforts to reach Sustainable Development Goal targets are significantly off-track. Efforts to improve newborn survival have also plateaued, with approximately 6,400 newborn deaths still occurring every day.

Hypertensive disorders are the most common medical problem arising during pregnancy, **and the second leading cause of maternal death globally** after postpartum haemorrhage. Pre-eclampsia/eclampsia (PE/E) is the most serious of these disorders and is associated with the greatest preventable loss of life. Pre-eclampsia is a multiorgan disease process that is generally defined as the onset of high blood pressure (BP) any time after 20 weeks' gestation accompanied by proteinuria (protein in urine). PE can progress rapidly and unpredictably and if not appropriately identified and managed, PE can develop into eclampsia – convulsions or seizures before, during and after delivery.

Pre-eclampsia (PE) complicates between 3% to 5% of pregnancies worldwide and is responsible for 76,000 maternal deaths and 500,000 fetal and newborn deaths annually, including 200,000 stillbirths. It is associated with babies born with low birth weight and causes up to 20% of the 13 million preterm births that occur each year. PE has an intergenerational impact as well, with women who experience PE at risk of severe life-long morbidity (e.g., hypertension, kidney disease, metabolic disorders, cardiovascular disease, anxiety and dementia), and infants born too small or too soon more likely to have life course complications and higher risk of non-communicable diseases decades later.

In the past 30 years, the incidence of pre-eclampsia has increased by 11% globally. This is due to many factors including the rise of non-communicable diseases, like chronic hypertension, obesity, and diabetes, which increase risk. Climate change is also increasing vulnerability in many direct and indirect ways. For instance, salinity in drinking water is associated with increased risk of PE/E and gestational hypertension, which is a growing concern given the pace of sea level rise and coastal flooding in some settings. Heat extremes and consequences of poor air quality also increase the risk of PE, fetal growth restriction, stillbirth and perinatal mortality. In addition, extreme weather events and forced migration can lead to delays in receiving appropriate care and essential interventions for detecting and managing pre-eclampsia.

Barriers to PE care

In LMICs, pre-eclampsia outcomes are impacted by delays in identifying and managing women at risk, the availability and quality of essential diagnostics and drugs, and gaps in health workers' knowledge and adherence to recommended practices, resulting in adverse outcomes. The primary clinical indicators of pre-eclampsia are proteinuria (protein in urine) and high BP, but there are numerous gaps impacting testing access. BP measurement is often inconsistent in these settings, with devices frequently broken, missing, or in use elsewhere in a health facility. Mercury sphygmomanometers are being phased out due to toxicity concerns, and other manual devices are inaccurate without frequent calibration and maintenance. Urine dipsticks are commonly recommended in country guidelines for detecting proteinuria, but their accuracy is low and lab-based tests are costly, complex, and infrequently available.

For management of pre-eclampsia risk, WHO recommends low-dose acetylsalicylic acid (aspirin, 75 mg/day) during pregnancy for the prevention of pre-eclampsia as well as antihypertensive drugs for women with severe hypertension. However, for aspirin to be an effective prevention measure for at-risk women, it should be prescribed before 16 weeks gestation, and many women in LMICs do not present this early in pregnancy for antenatal care. In some settings, aspirin is available only in large tablet sizes (300mg), which require cutting and reduce adherence. Timely access to antihypertensives is critical to controlling BP and preventing risk of pre-eclamptic seizures and strokes. Every health facility should have adequate oral and intravenous antihypertensive drugs in the antenatal, labor, and maternity units, but gaps in availability can limit access, and specific antihypertensives shown to be safe in pregnancy must be used. In addition, there are quality issues with aspirin and antihypertensive drugs available in LMICs, including substandard and falsified medical products.

In populations with low dietary calcium intake, WHO recommends daily calcium supplementation for pregnant women to reduce the risk of pre-eclampsia. However, barriers include the relatively high cost of calcium supplements, quality issues, and adherence challenges.

Magnesium sulphate ($MgSO_4$) is recommended to prevent and manage eclamptic seizures. $MgSO_4$ is cheap, heat stable and proven to be effective, but administration challenges limit use. The dosing regimen is complex, and although potential risks of toxicity are extremely rare, health care workers are often reluctant to administer it. Gaps in availability also limit uptake, with a recent survey finding $MgSO_4$ only regularly available in 45% of countries in the public sector and 58% in the private sector. In addition, $MgSO_4$ has supply risks due to a concentrated supply base, shorter expiration dates, and limited sources of quality product reported.

Summary of barriers affecting access to pre-eclampsia products and their implementation

- Quality: Low accuracy of available diagnostics (urine dipsticks, BP devices), including devices that require frequent maintenance and are not validated for use in pregnancy; Evidence of poor-quality medicines (aspirin, antihypertensives, $MgSO_4$), including substandard and falsified products.
- Supply and Delivery: Gaps in product availability due to supply chain weaknesses and poor coordination, and a concentrated supply base for some products.
- Demand and Adoption: Low antenatal care attendance and late presentation to care; gaps in health care worker knowledge and adherence to guidelines; low uptake of some WHO recommendations; competing priorities at the national and global-level and a need for evidence on effective, locally-tailored models of care.
- Innovation and Availability: Lack of funding and attention given to R&D to advance maternal health products due to perceived low return on investment.

4. Potential opportunities to improve pre-eclampsia risk detection and management

The most transformative shift in pre-eclampsia risk identification and management in recent years has been the introduction of biomarker-based testing in high-income settings. Pre-eclampsia is becoming increasing recognized as a progressive disorder manifesting as a state of imbalance in angiogenic factors (molecules that are fundamental to the process of blood vessel formation and vascular development of the

placenta). These indicators of placental dysfunction are detectable with biomarker-based tests and provide useful clinical information to guide care decisions at different points in pregnancy.

Two biomarkers hold significant potential for use both individually and as a ratio in various testing formats, including point-of-care (POC), and near POC tests. The first is placental growth factor (PlGF), a protein which is found to be decreased in women both at the time of diagnosis with pre-eclampsia and in advance of onset, as a predictive marker. A second marker, soluble fms-like tyrosine kinase (sFlt-1), is a protein that is predictive of pre-eclampsia when concentrations are elevated. To date, WHO has not updated its PE guidelines to incorporate markers of angiogenic imbalance, but professional organizations like the International Federation of Gynaecology and Obstetrics (FIGO) and the International Society for the Study of Hypertension in Pregnancy (ISSHP) have recommended the use of PlGF and sFlt-1 as a "rule out" tool to assist with triaging women and in timing delivery. More evidence is needed on how best to introduce biomarker-based testing in LMICs to inform clinical guidance and WHO recommendations. Supply-side engagement with test manufacturers is also needed to address affordability concerns and improve supply security.

Blood pressure measurement devices are essential for diagnosis and monitoring of pregnant women at risk, but devices are often unavailable and inaccurate, due to calibration and maintenance requirements. Affordable, automated BP devices offer potential to improve availability and measurement accuracy, but they were developed for use in non-pregnant adults. Further validation to ensure precise readings in pregnant populations is needed to improve availability and diversify the supply base. Other BP measurement innovations offer additional high-value features, such as the CRADLE VSA device, which incorporates a traffic light warning system that alerts health care providers to the need for escalated care. Studies using the device in LMIC settings have shown an association with reduced eclampsia and maternal death, but efforts are needed to drive demand and adoption. Digital tools such as OptiBP™ provide BP measurement using a mobile phone camera and have the potential to integrate with electronic clinical support systems to guide antenatal care. These tools could offer tailored and integrated solutions for countries following further validation.

While diagnostic products are a critical component, a comprehensive and holistic care package is needed to drive reductions in maternal and newborn deaths associated with PE/E. Efforts to refine optimal packages of interventions for PE risk detection and management for use in different contexts will be critical. There are opportunities to convene partners around development of a "PE/E care bundle," as this has been shown to be an effective approach in prevention and treatment of post-partum haemorrhage, and in sepsis prevention. Care bundles include a set of evidence-based practices that improve patient outcomes. Overcoming barriers to scale for other innovative delivery models should be considered as well, such as Group ANC and self-care approaches that are women-centered and shown to increase knowledge and adherence to treatments. Midwife-led models of care also offer promise, with the recognition that a well-trained and resourced midwife can promptly diagnose and initiate timely treatment. Similarly, addressing knowledge gaps on appropriate administration of timely antihypertensives and $MgSO_4$ can support healthcare providers' adherence to recommended practices and result in better health outcomes.

Innovative supply models, including regional manufacturing, hold promise for overcoming challenges with product stockouts and procurement of low-quality products. A recent systematic review found evidence of poor quality for eight PE products (magnesium sulphate, aspirin, calcium supplements, and multiple antihypertensives).[1] The identification of manufacturers with quality-assured products or through regional harmonization mechanisms should be explored to improve the supply base of quality products. There are opportunities to provide technical assistance to manufacturers in exchange for access commitments and to support post-market quality surveillance initiatives. Innovative financing mechanisms that match domestic financing contributions for quality assured commodities, such as the UNFPA Supplies Match Fund, may also be leveraged.

Finally, new product development on priority tools to guide clinical management of high-risk pregnancies could complement efforts to improve access to existing and emerging tools. Accurate and robust portable ultrasound devices and innovations for measuring gestational age would be transformative in better identifying pregnant women and fetuses with risk factors. Given that women in LMICs often present late for

[1] Maharjan P, Ponganam MP, Lambert P, et al. The quality of medicines for the prevention and management of hypertensive disorders of pregnancy: A systematic review. *PLOS Glob Public Health*. 2024;4(2):e0002962.

their first ANC visit, assessing gestational age can be challenging and there are missed opportunities to better manage potential risk factors. Opportunities to advance and evaluate different hand-held, lightweight, and low-cost ultrasound devices that are fit-for-purpose should be explored, given their strong potential to inform care in LMICs.

5. Partner engagement

Urgency to catalyze uptake of lifesaving PE tools is growing. Countries are increasingly prioritizing efforts to address PE in their Ending Preventable Maternal Mortality/Every Newborn Action Plan (EPMM/ENAP) Acceleration Plans. Through engagement with country, community and civil society partners, including women's advocacy groups, the importance of addressing PE is strongly acknowledged – and while many welcome the attention and growing momentum to address PPH, there is a clear desire to see PE/E prioritized to the same extent and to ensure that interventions are women-centered and locally tailored.

At the global level, there are opportunities for Unitaid to co-convene a Pre-eclampsia Summit with WHO and other partners to align on a roadmap to accelerate progress against PE. WHO is also interested in revising its guidance on PE diagnosis, taking into account the evidence in support of biomarker-based testing. Further evidence to shape WHO operational guidance will be needed, including a more comprehensive understanding of contextual factors influencing the clinical utility and effectiveness of these diagnostic aids. There are also opportunities for Unitaid to work with the relaunched UN Commission on Lifesaving Commodities for Women and Children's Health, including on essential commodities like $MgSO_4$ for PE/E. In addition, as Unitaid considers the implications of climate change on PE within its Climate and Health Strategy, there will be opportunities to align priorities and complement work underway by partners, including the WHO REACH (Research for Action on Climate Change and Health) program, Wellcome Trust, and others.

Other key funding organizations, such as Merck for Mothers and the Bill and Melinda Gates Foundation, have made significant investments in PE/E. Merck for Mothers is funding WHO to investigate the potential for a simplified $MgSO_4$ regimen to prevent eclamptic seizures and stroke and improve clinician adherence. The Bill and Melinda Gates Foundation is supporting the Preventing pre-eclampsia: Evaluating AspiRin Low-dose regimens following risk Screening (PEARLS trial) led by the Concept Foundation and others. The trial will compare the effects of 75 mg and 150 mg daily aspirin in Ghana, Kenya, and South Africa, following screening for PE risk. The Gates Foundation has also funded efforts to map the pipeline of drugs, therapeutics, and dietary supplements for PE/E under the Accelerating Innovation for Mothers project led by the Concept Foundation in partnership with the Burnet Institute. Many of these products are in early -stage R&D, but Unitaid will continue to monitor the pipeline and track progress. One promising RNA-based therapy under development by Comanche Biopharma is soon to enter a Phase IIa trial and has been given fast-track status by the US Food and Drug Administration. In terms of product development of devices, the Gates Foundation has also made investments in portable ultrasound, including artificial intelligence-based tools that can be used by lower-skilled health workers.

Regarding scale-up, it will be crucial to actively involve national programs in the design and implementation of Unitaid projects focused on PE/E. This is essential for sustainability, particularly given that most maternal and newborn health services are primarily funded domestically. Close collaboration with partners such as the Global Financing Facility (GFF) will also strengthen the scalability pathway for PE/E products, including targeting inclusion of products and delivery strategies in GFF investment cases. The GFF is a country-led partnership, hosted by the World Bank, that supports countries to strengthen health systems and improve access to care through investment cases identifying priority reproductive, maternal, newborn, child, and adolescent health and nutrition areas and best buys. The investment cases are aligned to public and private financing, with GFF grants acting as an incentive to align domestic resources, development aid, private-sector financing, and funding from global health organizations to fund the prioritized health plan. Regular engagement with bilateral donors like USAID and FCDO that provide significant funding to maternal health programs will be critical to scalability efforts as well.

6. Opportunities for Unitaid investment

The Secretariat has identified near-term opportunities positioned for funding in the investment pipeline: in the 2025 baseline (6.1 – implementation) and upside (6.2 – product development). The opportunities are described below and then assessed using Unitaid's prioritization criteria in Section 7.

6.1 Implementation to drive adoption of optimized and locally tailored packages of care for PE risk detection and management within ANC programs

Large scale, multi-country implementation work is needed to drive adoption of PE risk detection and management tools within ANC programs. Building on the prioritized areas of work that will be identified in a co-convened Pre-eclampsia Summit and roadmap publication, Unitaid would be well placed to accelerate access to optimized and locally tailored packages of PE care for risk detection and management. On the demand side, this would include introducing and testing models of care in various geographies and levels of the health system, including in areas of high climate risk (e.g., extreme heat, flooding), to understand effective care approaches and build resilience. A key focus of product introduction efforts would be to facilitate uptake of biomarker-based testing to enable LMICs to more quickly benefit from the diagnostic advances that are underway in high-income countries. There will be opportunities for Unitaid to address research gaps on effective use cases and operational considerations with use of biomarker testing in LMICs, in line with the findings of WHO's planned evidence review. Direct engagement with test manufacturers on commitments to affordable pricing will be critical as well. Efforts to advance diagnostic innovations should be conceptualized as part of a care bundle, following further stakeholder engagement around essential components, including BP measurement, maternal history, aspirin for at-risk women, anti-hypertensives, and appropriate referral and management. Engagement with policymakers, clinicians, patient-advocates, and community members from LMICs will be essential to defining care bundles and other innovative delivery models to advance.

On the supply-side, there are clear opportunities to address challenges with poor quality medicines and availability. Supplier engagement to identify quality assured manufacturers or offer technical assistance to support cost and quality optimization could be considered, including opportunities to advance innovative supply models like regional manufacturing and regulatory harmonization initiatives. Efforts to include PE/E products in priority lists for regional and global pool procurement mechanisms is another promising approach to creating demand for quality-assured products as well as the implementation of minimum-quality requirements for procurement with donor and domestic resources. Support for the design and implementation of post-market quality surveillance mechanisms also holds promise for reducing the quantity of substandard and falsified products in circulation. Furthermore, to help address availability issues, supply chain mapping activities would help identify opportunities for improved coordination and increased efficiency in product procurement and distribution.

6.2 Product development to advance high-priority innovations and expand the supply base

Several high-priority areas for product development were identified during Unitaid scoping and will be captured in a forthcoming landscape publication on tools and delivery strategies for better addressing PE/E in LMICs. First on biomarker-based testing, there are opportunities to further develop and adapt point-of-care tests for use in low-resource settings to ensure a larger supply base of fit-for-purpose products. Access commitments, including on affordable pricing, will be pursued in exchange for product development support.

Accelerating development of handheld, low-cost ultrasound devices would be a transformative innovation for obstetric care in LMICs and there is an active pipeline of products to advance. Other innovations for gestational age assessment include digital tools for biomedical image analysis, including software that is app-based. These products require further validation and development in order to unlock their potential. Digital tools also have potential to embed within risk prediction algorithms and clinical decision support tools that are in development.

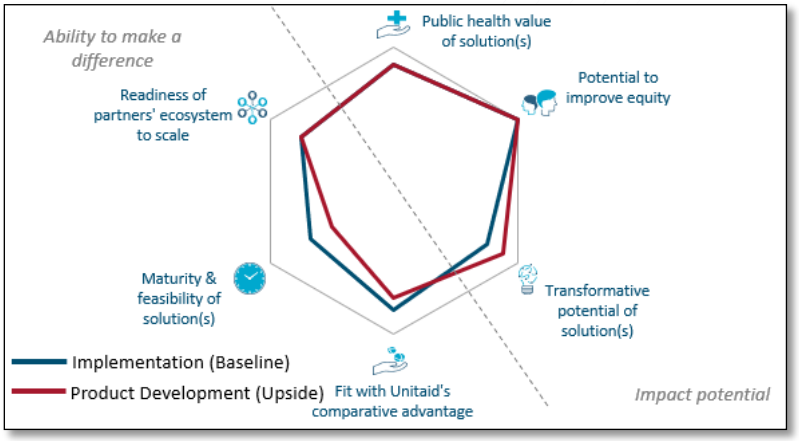
Efforts to ensure the availability of innovative and accurate BP measurement devices like the CRADLE VSA under opportunity 6.1 would be complemented by work to expand the supply base for quality automated devices that are validated for use in pregnancy. An investment in accuracy validation studies would be beneficial to facilitate identification of quality products and inform procurement decisions. This would also support countries to transition away from using BP devices with mercury, which are harmful to human health

and the environment, to safe, affordable, and accurate alternatives. Efforts in this area are well-aligned with Unitaid's initiative to advance climate-smart products.

7. Assessment of the opportunity

7.1 Impact potential, including the public health value of the solution, the potential to improve equity and the transformative potential of the solution

Given the significant maternal and newborn health burden caused by pre-eclampsia and strong potential to save lives, both opportunities have high scores for impact. Both include a strong emphasis on POC biomarker-based diagnostics, which have significant potential to enable improved risk detection and management of PE and improve access to new testing methods, currently only available in high-income settings. This is reflected in high scores for equity, as product implementation and development will be tailored to use in LMICs where these tools are needed most.



In terms of impact potential for the implementation opportunity, using the MANDATE model, Unitaid estimated that 44,000 maternal and newborn lives could be saved with better use of improved BP measurement devices like the CRADLE VSA (Unitaid 2020 Maternal Heath Area for Intervention). Both opportunities focus on biomarker-based testing and while cost-effectiveness evidence in LMICs is not currently available, findings from high-income countries have demonstrated cost savings due to reduced hospital admissions. Drawing on data from the US, the total cost burden of pre-eclampsia within 12 months of delivery amounts to $1.03 billion for mothers and $1.15 billion for infants annually.[2] While this data is not available for LMICs, it demonstrates the heavy financial toll placed on health systems and why early detection and management is so critical to avoid these costs.

For both opportunities their transformative potential lies in improving detection and management of PE, which would ensure access to necessary care, help avoid unnecessary referrals and hospital admissions, and save lives. The product development opportunity in the upside increases the transformative potential for this investment, particularly with efforts to advance portable obstetric ultrasound, as this is the cornerstone of modern maternity care. In addition, portable ultrasound devices offer benefits that go beyond pre-eclampsia and maternal care. There is also some evidence that use of ultrasound increases ANC attendance and facility delivery rates, leading to reductions in maternal and newborn mortality.

7.2 Ability to make a difference, including fit with Unitaid's comparative advantage, maturity and feasibility of the solution and readiness of partner ecosystem

The implementation opportunity shows a close fit with Unitaid's comparative advantage in deploying multi-country implementation projects to accelerate new product introduction, inform country scale-up, and generate demand. Unitaid is similarly well positioned to advance supply-side activities on quality medicines and innovative supply models. In addition, the opportunity strongly links with Unitaid's strategic initiatives on regional manufacturing and climate and health. The upside opportunity focuses on late-stage product development which is also well aligned with Unitaid's expertise, including work to accelerate development and adapt products for use in LMIC markets. Both PE opportunities would strategically complement the current PPH investments and support Unitaid's growing role in the maternal and child health space.

[2] Warren S, Shih T, Incerti D, et al. Short-term costs of preeclampsia to the United States health care system. *American Journal of Obstetrics & Gynecology*. 2017;217(3):237-248.

In terms of maturity of the solutions, the implementation opportunity in the baseline is clear, with biomarker-based tests available as well as other core components of the care package. In comparison, the upside opportunity on product development scores lower for the maturity of the solution, given the nature of this type of investment. Finally, both opportunities benefit from a strong partner ecosystem, with significant interest from the global, national, and community-level stakeholders to advance progress against PE/E.

7.3 Risk

For both opportunities, a key risk to accelerating use of biomarker-based testing in LMICs is the current lack of WHO recommendations on use of these tools. While plans for this evidence assessment are underway, Unitaid could mitigate this risk to the implementation opportunity by sequencing activities to support initial work on identification of care bundles in line with the anticipated PE roadmap, while WHO recommendations may advance.

As with any intervention that introduces tools that can enable early and appropriate management of disease, impact will depend on functioning health systems that are able to effectively refer and deliver appropiate care. To migitiate this risk for the implementation opportunity, Unitaid will pay close attention to country selection, and activities will include a focus on identifying health system requirements for effective implementation of a PE care bundle.

The upside opportunity on product development is inherently higher risk, with reduced capacity to deliver expected results. However, this risk can be mitigated with appropriate stage-gating in project design, and is counterbalanced by the strong benefits of increased supply security of the products in scope and the transformative potential of portable ultrasound.

From a scalability perspective, there are increased risks for maternal health products as compared to Unitaid's work in HIV, TB, and malaria, which have more established scale-up funding. The Secretariat will build on learnings from other activities in this space, including from its PPH and fever management portfolios, and work closely with scale-up funding partners throughout design and implementation of investments (e.g., USAID, Global Financing Facility). Most critical will be to ensure that all investments are country-led and embedded in the communities served. In addition, advocacy and domestic resource mobilization will be prioritized throughout Unitaid's work.