**Device – Target Product Profile (TPP)**

**Health/Disease Area: Pre-eclampsia**

**Intervention/Candidate: Risk screening tool**

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This is a draft document and is undergoing public consultation. It is anticipated that the contents and structure of this document may change during this process.

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1. **Background**
   1. **Pre-eclampsia**

Pre-eclampsia is a complication of pregnancy characterised by the presence of hypertension, proteinuria and/or end organ dysfunction, presenting after 20 weeks’ gestation.1 An estimated 4.6% of pregnant women each year will experience pre-eclampsia.2 Clinical manifestations of disease progression can include visual disturbances, headache, epigastric pain, thrombocytopenia, and abnormal liver or renal function. It can also lead to pulmonary edema, seizures, cerebral hemorrhage, hepatic failure, renal failure, and – if untreated - death. Additionally, the baby is at risk of adverse outcomes, particularly fetal growth restriction and preterm birth.3,4

Whilst the pathophysiology of pre-eclampsia is underpinned by abnormalities in the development of the placenta, the overarching trigger for abnormal placental development and the subsequent biological cascade of events remains poorly understood.5 Evidence suggests that a number of immunologic, genetic, environmental, obstetric, medical and sociodemographic risk factors may contribute to disease pathogenesis.4 Pre-eclampsia can present as late-onset disease (diagnosed at or after 34 weeks’ gestation or later),6 or as early-onset disease (diagnosed before 34 weeks’ gestation). The latter is less common, though associated with relatively higher risks of maternal and perinatal morbidity and mortality.7-10 As such, screening methods that can accurately identify women at increased risk of developing pre-eclampsia are essential. These would permit the timely initiation of preventative therapies (such as low-dose aspirin)as well as enhanced antenatal monitoring.11

Historically, pre-eclampsia risk screening has been based on selected maternal characteristics and past medical history to identify those at increased risk. While the risk factors used for risk stratification vary between guidelines, they often include maternal age >35 years, a previous history or family history of pre-eclampsia, presence of chronic hypertension and nulliparity.12,13 However, pre-eclampsia risk screening using maternal history alone does not appear to detect the majority of women at risk of pre-eclampsia.14,15

There are ongoing efforts to identify more accurate methods of pre-eclampsia risk screening. Single parameter methods use one type of test to determine risk for pre-eclampsia.16 For example, the use of blood or tissue samples for DNA profiling is being investigated for risk stratification as early as 9 to 14 weeks’ gestation.17

Other methods may use a combination of multiple types of tests to determine risk for pre-eclampsia, known as a multiparametric method. For example, data from maternal history, a biomarker test result (via blood or urine sample) and a machine-based test (eg. an ultrasound to measure uterine artery pulsatility index) can be combined using an algorithm to produce a woman’s risk level or risk score.

The Bayesian model developed by the Fetal Medicine Foundation (FMF) is an example of a multiparametric test. It allows for estimation of an individual patient-specific risk estimate for preterm pre-eclampsia, using data on maternal characteristics and history, uterine artery pulsatility index (UtA-PI), mean arterial pressure (MAP), serum placental growth factor (PlGF) and/or pregnancy-associated plasma protein-A (PAPP-A).18 Use of this algorithm at 11- 13 weeks’ gestation in high-income countries has been shown to predict 90% of early pre-eclampsia, 75% of preterm pre-eclampsia and 41% of term pre-eclampsia, at a false positive rate of 10%.19 Another study has also shown similar results using this algorithm at 11-13 weeks’ gestation.20 This model has been independently validated in multiple settings.21

It is likely that additional innovations in predicting pre-eclampsia will emerge in the future. These innovations may include artificial intelligence-based risk assessments that combine multiple data sources. Whilst this may open new possibilities, it can also bring about new challenges such as data security issues. The outputs of an intervention – such as false positive or false negative results- can also pose different challenges on the health system including overloading secondary and tertiary level facilities due to erroneous high-risk assessment.

Despite the development of new pre-eclampsia risk screening approaches and technologies, using maternal history checklists remains routine practice in many settings. There are also multiple barriers to implementing certain pre-eclampsia risk screening methods at scale, particularly in limited-resource settings. The majority of women giving birth worldwide live in low- and middle-income countries (LMICs).22 However, in many LMICs, advanced laboratory testing and obstetric ultrasound is not routinely available in public antenatal care services, due to factors such as insufficient infrastructure, limited supplies, or limitations in the available health and laboratory workforce.23,24 Furthermore, many women in these settings do not commence antenatal care until the second half of pregnancy.25,26 Screening for pre-eclampsia risk – even using history-based risk factors alone - is not routinely performed in many LMICs.27 When it is performed, reliance on history-based risk factors will likely not identify the majority of women who are truly at risk.9 These realities mean that many pregnant women miss a critical opportunity for pre-eclampsia risk screening, as well as commencing preventive therapies as early as possible.

Innovations are needed to improve the options available to pregnant women for pre-eclampsia risk screening, especially in limited-resource settings. The development of this Target Product Profile (TPP) aims to inform and accelerate development of such innovations, to help prevent and mitigate the effects of pre-eclampsia globally.

* 1. **Purpose of this Target Product Profile**

TPPs are strategic documents that outline the minimum and optimal characteristics required for new health products, including medicines and devices. TPPs are an important resource to guide key stakeholders (such as funders, researchers, product developers, manufacturers and regulators) on the requirements of new medicines, diagnostics and devices to meet pre-specified clinical and public health needs.28 They inform research and development strategies, help frame product dossiers, streamline communication with regulatory agencies and help funders set targets.29

Availability of risk screening tools that can accurately predict which pregnant women will develop pre-eclampsia would facilitate the implementation of timely and targeted prevention strategies. However, there are currently no TPPs publicly available for risk screening tools for pre-eclampsia for pregnant women.30 As such, the development of this TPP provides clear guidance to help drive innovation, research and implementation of effective and accessible risk screening tools for pre-eclampsia to improve the health outcomes for women and newborns worldwide.

1. **Summary: Intervention Use Case and Target Users**

A screening tool that can be used to accurately predict which pregnant women are at high (or increased) risk of developing pre-eclampsia. This tool may constitute any method for pre-eclampsia risk screening and prediction, whether single parameter or multi-parametric test. Test results may also be combined in an algorithm to produce a woman’s risk level or score. This tool will be suitable for use during pregnancy as part of routine antenatal care, including in limited-resource settings. It will be used by a health worker in antenatal care services and would be user-friendly and affordable across a range of settings. Identification of women at increased risk of developing pre-eclampsia allows for preventive interventions, such as low-dose aspirin, to be commenced early and help prevent the onset of pre-eclampsia.

1. **Executive Summary: TPP Core Variables**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Minimum**  *The minimal target should be considered as a potential go/no go decision point.* | **Optimistic**  *The optimistic target should reflect what is needed to achieve broader, deeper, quicker global health impact.* | **Annotations**  *For all parameters, include here the* ***source data used and rationale*** *for why this feature is important.* |
| **General Scope** | | | |
| **Intended Use** | A tool for screening pregnant women to identify those at high risk of developing pre-eclampsia who can benefit from timely initiation of preventative therapies. | Same as minimum.  Plus:  Tool can predict and distinguish between onset of pre-eclampsia (such as early onset, late onset, preterm, term). | WHO currently recommends that pregnant women at moderate to high risk of developing pre-eclampsia should receive prophylaxis with daily low-dose (75mg) oral aspirin, ideally commencing before 20 weeks’ gestation.11 Low-dose aspirin has been found to reduce risk of pre-eclampsia (RR 0.82, 95% CI 0.77 to 0.88) and fetal or neonatal death (RR 0.85, 95% CI 0.76 to 0.95).31 |
| **Target Population** | All pregnant women, adolescent girls, and transgender and gender diverse people.  Tool can be used during pregnancy, including in the first trimester. | Same as minimum. | Risk screening for pre-eclampsia should be conducted for all pregnant women. In terms of ensuring benefit for screening, doing this as early in their pregnancy as possible - and ideally before 20 weeks’ gestation – is important.    However, some women will not have access to antenatal services in early pregnancy. Therefore, a risk screening tool should still be able to accurately predict risk of pre-eclampsia for women presenting to antenatal care later in pregnancy. |
| **Target Countries** | All countries, with a particular focus on limited-resource settings and regions with high rates of pre-eclampsia and/or poor maternal and neonatal health outcomes related to pre-eclampsia. | Same as minimum. | Pre-eclampsia can affect women in any setting or population, therefore this variable is not limited to certain countries. However, the highest rates of pre-eclampsia are observed in Africa, Europe and South-East Asia with incidence rates of 5.6%, 5.3% and 5.1% respectively.2  As such, risk screening methods must be applicable in high, medium, and low-resource settings. |
| **Target Users** | Tool can be used by a healthcare worker delivering antenatal care, including midwives, nurses, doctors or specialist obstetricians.    For some tools, laboratory staff may be required (for example if blood sample analysis is required). | Same as minimum.  Plus:  Tool can be used by community health workers and can be used at peripheral levels of health care in limited-resource settings. | Risk screening methods should be used by trained healthcare workers delivering routine antenatal care to pregnant women. However, the cadre responsible for providing this care may differ depending on the setting and country. Therefore, using the tool should not require the need for specialist training.  In many countries, a shortage of skilled health care workers as well as financial and geographical barriers, can prevent pregnant women from accessing and receiving healthcare.  Community health workers (CHWs) are often utilised to ensure that women in more rural or remote communities can access key healthcare interventions.32 CHWs strengthen antenatal care by identifying pregnant women, diagnosing selected pregnancy-related or pre-existing health conditions, and providing health promotion and disease prevention education.33 |
| **Tool – General Properties** | | | |
| **Design and functionality** | Design is user friendly, simple and quick to use with minimal steps to set up or operate.  Can be performed by an antenatal care worker across diverse settings. | Same as minimum.  Plus:  Tool can be used offline (i.e. active internet connection not required). | Across countries, a range of different health care worker cadres deliver antenatal care services and therefore the tool needs to be suitable for use across these cadres.  Continuous internet connection is not always certain in some settings, such as rural and remote locations. |
| **Acceptability** | Tool can be easily and feasibly integrated into routine clinical procedures in antenatal care settings. | Same as minimum. | Availability of a tool does not guarantee uptake within the setting, so the expectations and demands of local settings, users and pregnant women must be considered to ensure it is well received and to facilitate strong uptake. |
| **Tool Validation** | Tool (and its component test/s) have been developed in an evidence-based way, with robust, verifiable, peer-reviewed data demonstrating that it is valid and can accurately predict pre-eclampsia. | Same as minimum.  Plus:  Tool has been externally validated, independent of the test developer.  Tool has been externally validated in different settings and populations, including in LMICs.  Tool is being updated over time to improve its performance, in response to new data or evidence. | The minimum targets ensure that principles of content validity and construct validity are followed.34 Product developers must provide proof that a tool is based on evidence, is functional and achieves the intended use for the intended setting.  Demonstrated external validity ensures that the tool performs well in different contexts. |
| **Regulation** | Tool (where applicable) has requisite regulatory approval by relevant international authorities/agencies.  In countries where it is used, it is compliant with national regulatory agency standards.  If tool involves a medical device, it should meet international regulatory requirements and standards, including ISO 13485:2016, and/or are in accordance with current national guidelines. | Same as minimum. | Approval from regulatory agencies will ensure that the tool is compliant with local regulations, medical standards for design and manufacture, and safety requirements.35 |
| **Procurement Price** | Tool is available at low or zero cost.  If relevant, special tests or devices included as part of a tool are affordable to the public sector.  Tool is competitively priced relative to similar technologies in low-middle income markets. | Same as minimum.    Plus, for any special tests included within tool:  Bulk purchase discounts are available.  Local manufacturing possible. | Price is a vital consideration, and likely to vary by test type, quality and manufacturer. Prices may also vary across different countries.    In addition to wholesale test costs, additional expenses such as extra equipment (e.g. transducers for imaging tests), consumables, shipping, import permits, and maintenance (if applicable) must be considered. |
| **Primary Target Delivery Channel** | Tool can be used in a range of health facilities that provide antenatal care services, including tertiary or secondary level hospitals, or primary antenatal care clinics. | Same as minimum.  Plus:  Ability to offer service at community outreach settings. | To achieve health equity, risk screening tools should be able to be utilised across a range of settings where women access antenatal care, as well as different levels of healthcare (primary, secondary and tertiary).  If the tool requires the use of special tests or devices that require a laboratory, these requirements should be explicit. In this instance, laboratory requirements would need to be factored into scale-up efforts.  Some pregnant women in rural and remote communities may only have access to antenatal care services through community outreach programs. |
| **Packaging** | If tool includes special test/s or devices, those are easily packable.  Low environmental footprint with most of the packaging recyclable. | Same as minimum.  Plus:  All the packaging is recyclable. | The test/s within the tool should be easily packable to facilitate efficient shipping to any location. The packaging should reduce the risk of damage to the test during transit.    Environmental footprint and waste disposal should be considered and limited where possible, to address environmental concerns. |
| **Environmental stability** | If tool includes special tests or devices (including smart devices for operation), they are durable for use in all settings and can be stored and operated in a wide range of climatic conditions including heat, cold, moisture, dust and humidity. | Same as minimum. | In some settings temperature control of tests or devices may not be consistently possible. They therefore need to be reasonably durable to ensure functionality and performance.  The stability of the tests or devices must be tested by operating them at different climatic conditions. |
| **Training Requirements** | Quick guide and user manual provided with tool, in relevant language/s used by healthcare workers in local context.    Supplementary single-session, online, on-demand training (such as checklists, videos, guides) provided. | Same as minimum.  Plus:  Quick guide and user manual provided for users, in relevant language/s for local context, plus translations into all official UN languages. | Each test within the tool will have its own specific training requirements which must be adhered to.    Appropriate and easy to understand training and user manuals are necessary for any specific test.  Where possible, guidance for use and interpretation of results should include images and text. |
| **External Support** | Phone number provided to seek assistance with tool online or remotely. | Built-in access to online/remote expert advice to assist tool operation via SMS, audio call or video conferencing. | The provision of external technical support to perform troubleshooting will enhance user experience and allow for timely solutions.  Given that internet and reception may not always be guaranteed where the tool is used, a FAQ sheet listing commonly encountered problems and steps to resolve them should be provided. |
| **Tool – Tests and Outputs** | | | |
| **Device-based technologies** | *If device-based technologies are used:*  Can be transported, assembled and performed by one person.  No more than three operator steps that are not timed nor labour intensive.  Reusable equipment.  If non-rechargeable battery used, it has back up battery power lasting minimum 45 minutes or if rechargeable integrated battery used, has minimum 5 hours on a single charge.  Auto sleep/shut-off capabilities for battery saving.  Results are easily readable. | *If device-based technologies are used:*  Can be transported, assembled and performed by one person.  No more than one operator step that is not timed nor labour intensive.  Reusable equipment using energy efficient technology.  Back up battery power lasting minimum 2 hours, or rechargeable integrated battery with minimum 8 hours on a single charge. Auto sleep/shut-off capabilities for battery saving.  Results are easily readable. | The minimum and optimal requirements are in relation to the test operation only and do not include additional requirements that may be necessary for sampling or sample storage.  When running off battery power, notifications are necessary to alert the user of low battery to prevent the device shutting down while in use. |
| **Sample types, collection and processing** | If a sample is required, collection is minimally invasive - relative to alternative methods that can be used – and requires minimal equipment to obtain sample.    Minimal sample processing which does not require laboratory or cold chain. | No sample required as part of tool. | Whilst biomarker testing for PlGF and sFlt-1 requires venous blood and requires needles, biomarker testing for glycosylated fibronectin uses capillary blood and requires a finger prick only.36 Thus, using capillary blood is less invasive and painful compared to blood sampling via needles.  Access to and availability of laboratory facilities and personnel may be limited in low-resource settings.  If a blood test is required, it would be advantageous to do the test on whole blood rather than serum so that a centrifuge is not needed. |
| **Point of care tests** | *If point of care tests are used:*  Single use, disposable test that adheres to ASSURE criteria. | Same as minimum.  Plus:  Test is biodegradable or recyclable. | ASSURE criteria, established by the WHO, has become a benchmark for an ideal test that can be used at the point of care to ensure utilisation at all levels of the healthcare system.37  Biodegradable and recyclable materials will ensure that the test is environmentally friendly. |
| **Clinical Specificity and Sensitivity** | Sensitivity >70%    Specificity >60% | Sensitivity >90%  Specificity >60% | Having a high sensitivity for screening tests is essential to capture the greatest proportion of true positives out of all people with the condition.  Using maternal factors only for pre-eclampsia risk screening – such as the NICE guidelines – was reported to detect 39% of women experiencing pre-eclampsia < 37 weeks with a false-positive rate of 10.2%.  By comparison, the FMF model at 11-13 weeks of gestation - using maternal factors, PlGF, MAP and UtA-PI - reported a sensitivity of 90% for early pre-eclampsia, at a screen positive rate (SPR) of 10%.19 |
| **Safety** | Target Population  Tool will have no or minimal adverse health or safety outcomes for pregnant women.  The test/s within a tool has/have no teratogenic or abortive properties posing risk to the fetus or neonate.    Target Users  Standard biosafety requirements to be followed by target users.  No adverse health or safety outcomes for target user. | Same as minimum. | There have been no documented reports of adverse fetal effects for diagnostic ultrasonography procedures, including duplex Doppler imaging. However, it is advised that ultrasound imaging be performed efficiently and only when clinically indicated to minimise fetal exposure risk using the keeping acoustic output levels As Low As Reasonably Achievable (commonly known as ALARA) principle.38    Biomarker testing including DNA analysis via blood sampling or urinalysis during pregnancy is widely used to determine risk for various antenatal conditions and is safe for mother and fetus.    There may be associated adverse effects with performing DNA analysis via tissue sampling depending on the site and hence it is recommended that these techniques are carefully considered.  Other emerging technologies which can predict risk of pre-eclampsia should be carefully assessed to ensure they are meeting optimal safety requirements. |
| **Calculation of risk** | Tool stratifies women into 2 or 3 risk groups only (Such as low, medium or high risk). | Tool calculates a specific quantifiable risk score or value for an individual woman.  Risk assessment can be updated during the course of pregnancy. | A quantifiable risk score or value will better guide clinical practice. |
| **Results** | A clear high risk, low risk or invalid result with clear and simple instructions for interpretation. | Same as minimum.  Plus:  Quantifiable value/risk score is provided. | Results must clearly show a level or score of risk of pre-eclampsia.    Ideally, the tool result is easily understood and acted upon by healthcare workers, thus supporting clinical decision-making. |
| **Time to result** | Tool produces a result within a single antenatal care visit. | Tool produces a result immediately. | Time to result should be as short as possible and in line with the manufacturer’s recommendations.  If the tool includes multiple tests, these will each require time to obtain results, which then need to be inputted into the tool (or algorithm).  Point-of-care testing reduces the time to obtain test results and expedites the diagnosis and initiation of treatment. This is particularly critical in settings with limited healthcare infrastructure and barriers to accessing quality and timely medical care. |
| **Tool Recommendations** | Tool provides a risk level or score only. | Same as minimum.  Plus:  Tool provides patient management recommendations, based on evidence-based guidelines, according to the risk level or score. | WHO recommends that women at high-risk of developing pre-eclampsia should be offered low-dose aspirin.11  WHO also recommends that calcium supplementation can help prevent pre-eclampsia in women with low calcium intake.39  Additional monitoring is required once women begin these preventative therapies and therefore the availability of required resources (staffing, medical supplies/devices) must be considered. |
| **Data** | | | |
| **Data input** | If tool requires data entry, manual data entry is performed by target users. | Integration/ utilizing electronic patient data from existing health information systems.  Data can be stored on database when offline and synchronized once internet is available. | Methods of data input that are more time efficient are preferable.  The ability to store data offline, which can be synchronized once internet is available ensures that data can be captured anywhere and limits the need for paper records which may increase the risk of human errors and losing data.  Utilizing and updating patient information on local health information systems as part of the tool will allow for a health-systems strengthening approach. |
| **Data security and privacy** | If tool stores patient sensitive information, it operates under secure connectivity which meets data protection and regulations of individual countries to avoid loss and corruption of sensitive data, and mitigate cyberattacks, whether data are at rest or in transmission.  Tool minimizes as much as possible the use of sensitive data. | Same as minimum. | ISO 27001 should be adhered to if no national data security policies exist. This will ensure that data integrity is preserved, risks are identified and mitigated, and relevant security processes are established.  International transmission of data should be minimized. |

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