GLOBAL CALL FOR DATA FOR PRE-ECLAMPSIA
Concept Note

1. BACKGROUND

The UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Sexual, Reproductive, Maternal, Child and Adolescent Health and Ageing, World Health Organization, is the main instrument within the United Nations system for research in human reproduction, bringing together policy-makers, scientists, health care providers, clinicians, consumers and community representatives to identify and address priorities for research to improve sexual and reproductive health. Since 1972, HRP has been at the forefront of research for sexual and reproductive health and rights.

Hypertensive disorders of pregnancy, particularly pre-eclampsia and eclampsia, remain important causes of maternal and newborn mortality, severe morbidity and long-term disability worldwide.[1,2] Pre-eclampsia is a heterogeneous, multisystem disorder with considerable variation in its clinical presentation, progression and prognosis. Although traditionally defined by new-onset hypertension after 20 weeks of pregnancy accompanied by proteinuria, contemporary definitions increasingly recognize the diagnostic role of maternal haematological, hepatic, renal, respiratory and neurological dysfunction, as well as uteroplacental dysfunction, fetal growth restriction and angiogenic abnormalities. Contemporary definitions differ in their diagnostic components and thresholds, classification of onset and severity, use of placental and angiogenic biomarkers, and incorporation of chronic hypertension and other comorbidities.[3,4]

The biological processes leading to pre-eclampsia may begin well before the clinical manifestations required for diagnosis become apparent. Maternal demographic, medical and obstetric characteristics are already used to identify women at increased risk, while clinical, biochemical and ultrasound markers such as blood pressure, pregnancy-associated plasma protein-A (PAPP-A), soluble fms-like tyrosine kinase-1 (sFlt-1), and uterine artery Dopplers may provide additional prognostic information. However, existing risk-assessment strategies and prognostic models vary in performance and applicability, and the incremental value of these markers beyond maternal characteristics remains uncertain.[3,4]

In recognition of the growing need for global action to improve the prevention and care of hypertensive disorders in pregnancy, and as part of WHO's efforts to develop up-to-date and universally acceptable norms and standards, WHO has embarked on a rigorous process for the reappraisal of the definition of pre-eclampsia and risk assessment strategies as fundamental requirements towards improving care and outcomes globally. Large contemporary cohorts and trials provide an opportunity to evaluate candidate markers across diverse settings and populations, and harmonization of individual participant data (IPD) permits consistent definitions, evaluation of

multiple thresholds without relying on published categories, and assessment of incremental prognostic value using combinations of markers.

2. OBJECTIVES OF THE PROJECT

WHO aims to achieve the above goal by embarking on a multi-step process that includes syntheses and review of the up-to-date research evidence base underpinning both the definition of pre-eclampsia and the identification of women at increased risk of subsequently developing pre-eclampsia with the aim of reaching scientific consensus through external technical consultations.

Objective 1. Definition and diagnostic framework

To reappraise the definition and diagnostic framework for pre-eclampsia by evaluating whether candidate clinical, laboratory, maternal organ-dysfunction, uteroplacental, fetal and placental markers, individually or in combination with hypertension and/or proteinuria, improve identification of women at risk of adverse maternal and perinatal outcomes, and by examining clinically relevant thresholds, combinations and timing of markers.

Objective 2. Risk stratification before disease develops

To evaluate the prognostic accuracy and applicability of strategies for identifying pregnant women at increased risk of subsequently developing pre-eclampsia, among women who have not developed pre-eclampsia at the relevant marker assessment. Analyses will assess individual markers and combinations to assess if eligible markers improve prognostication beyond maternal and clinical factors alone for subsequent pre-eclampsia at different gestational ages.

3. CHARACTERISTICS OF THE REQUIRED DATA

Studies (datasets) must meet mandatory criteria to be included in the pooled database. The criteria are listed in Box 1. A dictionary containing all variables and the study protocols or main manuscripts must be provided. Data collected from routine or administrative systems will be accepted only upon submission of the data collection protocols or other detailed description of data collection methods. Data obtained for this project will be harmonized and pooled into a global cohort.

Box 1. Summary of the study-level eligibility criteria to be included in the pooled database

1. Ethics and governance	Data were collected under appropriate research ethics committee or equivalent approval, or an ethics exemption was obtained, as applicable. The data holder and institution must be able to enter into an agreement with WHO permitting secure transfer and prespecified analysis of de-identified data.
2. Standardized data collection	Data were collected using a standardized research protocol or during a clinical or public-health care encounter, with adequate documentation of collection methods.
3. Eligible designs	Prospective or retrospective observational cohorts; cohorts nested within randomized or non-randomized intervention studies; administrative or clinical databases; and trial datasets in which eligible predictors/markers and outcomes were measured.

4. Population	General or unselected pregnancy cohorts; cohorts enriched for women at increased baseline risk; women screened, tested or assessed because pre-eclampsia was suspected; and cohorts of women diagnosed with pre-eclampsia where relevant to definition or severity analyses.
5. Sample size	Datasets should include more than 200 pregnant women who were screened, tested or assessed with the intention of diagnosing pre-eclampsia, including women at risk of, suspected to have, or diagnosed with pre-eclampsia. Cohorts restricted to women diagnosed with pre-eclampsia may contribute to severity analyses but not to analyses that require an unselected or pre-disease population.
6. Individual-level data and timing	IPD must include sufficient information on gestational age and the timing of predictor or marker measurement and outcomes to establish the required temporal relationship. For risk-assessment analyses, women must not have pre-eclampsia at the relevant marker assessment.
7. Markers/predictors and outcomes	Data must include at least one eligible candidate marker, predictor or reconstructable strategy and at least one outcome relevant to the objective to which the dataset will contribute.
8. Historical definitions	Datasets are not required to have used a particular historical definition of pre-eclampsia, provided the definition used can be identified or reconstructed sufficiently for the planned analysis.

Candidate markers and outcomes

Candidate markers: studies of pregnant women that have gathered one or more candidate markers measured with the purpose of risk-assessment or diagnosing pre-eclampsia:

- **Maternal characteristics**: age, ethnicity, body mass index, chronic hypertension, diabetes, renal disease, autoimmune disease and other relevant demographic or medical history.
- **Obstetric and pregnancy characteristics**: parity, previous pre-eclampsia, family history, multiple pregnancy, assisted conception and other relevant pregnancy characteristics.
- **Clinical markers**: Blood pressure and mean arterial pressure, clinical symptoms, including neurological or visual symptoms and right upper quadrant or epigastric pain.
- **Maternal organ-dysfunction markers:** proteinuria assessed by dipstick, protein-creatinine ratio, albumin-creatinine ratio or 24-hour collection, platelet count, aspartate and alanine aminotransferases, bilirubin, serum creatinine, estimated glomerular filtration rate, oxygen saturation and pulmonary oedema.
- **Angiogenic and placental markers**: PAPP-A, PlGF, sFlt-1, sFlt-1 to PlGF ratio and other placental markers.
- **Other biological markers**: endothelial, inflammatory, immune and metabolic markers.
- **Imaging markers**: uterine artery Doppler, maternal ophthalmic artery dopplers and other maternal, placental, fetal and ultrasound measures.
- **Risk assessment or prediction strategies**: combinations of markers and existing multivariable prediction models assessed before development or at the time of diagnosis of pre-eclampsia.
- **Medication and treatment use**: aspirin, calcium, antihypertensives, antenatal corticosteroids (ACS), tocolytics and magnesium sulfate.

AND

Clinical outcomes: Studies should also report clinical outcomes occurring in pregnancy or peripartum and around hospital discharge.

- Subsequent development of pre-eclampsia, and superimposed pre-eclampsia.
- Gestational age at birth, mode of birth and birthweight.
- All-cause maternal mortality, eclampsia, HELLP syndrome, severe hypertension, stroke, pulmonary oedema, acute kidney injury or kidney failure, hepatic complications, postpartum haemorrhage, intensive-care admission, and organ support.
- Fetal or neonatal death, preterm birth before 34 weeks, small for gestational age, severe neonatal morbidity, and neonatal unit admission.
- Chronic hypertension, kidney failure, and other comorbidities, where available and sufficiently comparable.

Other important variables that are not listed above, will also be extracted from the available data if relevant.

The lists of variables and their description are available in the Data Sharing Standards (DSS).

4. Procedures for data sharing

The principal investigator (PI) interested in sharing the data must complete an online screening form providing information on the study eligibility criteria and the responsible PI. After the revision of the forms, WHO will contact the PI responsible for those approved datasets and invite them to proceed with data sharing. The PI will need to sign a standard data-sharing agreement included in the DSS, and the data-sharing process will adhere to standard and safe procedures also outlined in the DSS. PIs will be asked to de-identify data and remove information that could lead to identification of individuals. WHO will manage the data repository and have access to the shared datasets. The PIs collaborating with this project will have access to their own raw data. WHO will only use the data to achieve the goals of this project (i.e., it will not be used in other projects nor to answer other questions). The management of the repository and any updates will be the sole responsibility of WHO. In addition, datasets will not be retained beyond the dates outlined in each data sharing agreement. All potentially eligible data will be sought irrespective of the data that were included in the published reports. This project may contribute to global guidelines on the care of hypertensive disorders in pregnancy.

5. Steps to be taken with the shared datasets

Each shared dataset will be rigorously cleaned and harmonized, including assessment of biologically implausible values. This process will ensure that the data from different sources are standardized and will be potentially combined into a unique database. The overall tasks involved in the data harmonization process comprise, but are not limited to, the following activities:

1. Data completeness checks with the revision of the incoming data (completeness in terms of documentation and variables needed).
2. Data monitoring after the data are transferred to the designated repository, with the programming group working with the contributors to resolve data-related queries.

3. Programming activities include creating programming practices, working with analysts on creating and modifying specifications, data reproducibility, code generation, and review.
4. Data corrections and finalization, including working with the analysts to make modifications and corrections where needed.

After the datasets are harmonized and combined, the data analyses will consist of several steps. Data with different measurement units will be converted according to the international system of units, and derived values will be computed where their components are measured contemporaneously. For markers measured at several time points, such as blood pressure, measurements coinciding with antenatal visits and around the time of diagnosis will be extracted. The prognostic accuracy of each candidate marker will be estimated across thresholds, and methodological quality will be assessed using the Quality Assessment of Prognostic Accuracy Studies (QUAPAS) tool.[5] The heterogeneity of key variables across datasets and countries will be carefully considered. Different modelling strategies will be considered, with the final model selected based on both clinical and statistical considerations.

For any inquiries about the repository or data, please contact us at PEDefinitionProject@who.int.

6. How will I be acknowledged for sharing my data?

By actively participating in data sharing, you will contribute to the collective knowledge base and enhance our understanding of pre-eclampsia. Principal Investigators providing data that is used in a specific analysis will be considered for participation in the writing group of any publication and potentially be included as a named author on any data synthesis manuscripts.

References

1. World Health Organization. Trends in maternal mortality 2000 to 2020: estimates by WHO, UNICEF, UNFPA, World Bank Group and UNDESA/Population Division. Geneva: World Health Organization; 2023.
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3. Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018;72(1):24–43.
4. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis and management recommendations for international practice. Pregnancy Hypertens. 2022;27:148–169.
5. Lee J, Mulder F, Leeflang M, Wolff R, Whiting P, Bossuyt PM. QUAPAS: an adaptation of the QUADAS-2 tool to assess prognostic accuracy studies. Ann Intern Med. 2022;175(7):1010–1018.