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Global Inequities in Preeclampsia Research: A Scoping Review and Landscape Analysis of Drug Repurposing Clinical Trials (2000–2025)

Sergio David Angulo Montaño

sdangulo81284@umanizales.edu.co

Caja de compensación familiar de Risaralda - Salud comfamiliar

Sandra Olaya

Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas Institución Universitaria Visión de las Américas

Juan Diego Trujillo

Universidad de Manizales, Facultad de ciencias de la salud

Isabella Montealegre

Universidad de Manizales, Facultad de ciencias de la salud

Julián David Toro

Caja de compensación familiar de Risaralda - Salud comfamiliar

Samy Giraldo

Universidad de Manizales, Facultad de ciencias de la salud

Silvana Castaño

Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas Institución Universitaria Visión de las Américas

Isabella Vidal

Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas Institución Universitaria Visión de las Américas

Tatiana Perdomo

Universidad de Manizales, Facultad de ciencias de la salud

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Global Inequities in Preeclampsia Research: A Scoping Review and Landscape Analysis of Drug Repurposing Clinical Trials (2000–2025)

Authors: Sergio David Angulo [a] , Sandra Olaya [a,b,c], Juan Diego Trujillo [c], Julián David Toro [a], Isabella Montealegre [c], Tatiana Perdomo [c], Samy Giraldo[c], Silvana Castaño[b], Isabella Vidal[b].

Affiliations:

a) Caja de compensación familiar de Risaralda - Salud comfamiliar, Pereira,Risaralda, Colombia
b) Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas Institución Universitaria Visión de las Américas, Pereira, Colombia
c) Universidad de Manizales, Facultad de ciencias de la salud

Corresponding author: . Address: Clínica Comfamiliar Risaralda – Salud Comfamiliar, Teaching and research unit (UID), Morito City Country House 99, Pereira, Risaralda 660001, Colombia. Tel.: +57 3145098175.E-mail: sdangulo81284@umanizales.edu.co (S.D. Angulo).

Abstract

Background: Preeclampsia (PE) remains a leading cause of maternal mortality globally. Yet data on trial representation across regions and populations are limited, raising concerns about equity and inclusivity in research.

Methods: We performed a scoping review and landscape analysis of ClinicalTrials.gov and WHO ICTRP registries (January 1, 2000–December 31, 2025). Interventional trials testing non-standard pharmacological agents for PE were included. Data were stratified by country, income level, and Maternal Mortality Ratio (MMR). Spearman's rank correlations were used to assess associations among research activity, national wealth (GDP), and clinical burden (MMR).

Results: From 1,765 records, 47 trials met the inclusion criteria. Metformin was most studied (n=15; 31.9%), followed by statins (n=11; 23.4%) and esomeprazole (n=9; 19.1%). High-income countries (HICs) hosted 51.1% of trials (n=24) despite the lowest MMRs. Iran (n=9; 19.1%) and

Egypt (n=7; 14.9%) led globally, outpacing the United States (n=5). No significant correlations emerged between trial numbers and GDP (r_s=0.40; p=0.06) or MMR (r_s=0.21; p=0.33). Public/academic funding dominated (93.6%; n=44), with minimal industry involvement (6.38%; n=3).

Keywords: Preeclampsia, Drug Repositioning, Global Health, Clinical Trial, Health Equity, Maternal Mortality.

1. **Introduction**:

Preeclampsia (PE) is a hypertensive disorder of pregnancy that affects approximately 4.43% of gestating patients globally (1). As a primary cause of maternal and fetal morbidity, this pathology is responsible for nearly 14% of maternal deaths worldwide (2,3). However, a profound inequality exists in the global distribution of these outcomes. In high-income countries, such as Denmark, the incidence of preeclampsia is 2.6% to 3.7%, whereas in low- and middle-income countries (LMICs), such as Peru, the incidence exceeds 10% (1). This discordance reflects alarming deficiencies in healthcare infrastructure and access to quality prenatal care.

Current PE management focuses on blood pressure control with antihypertensives and seizure prevention with magnesium sulfate (3,5). However, no standard therapies address the underlying etiology, systemic endothelial dysfunction, and angiogenic imbalance (5,9). Due to this lack of innovation, PE has been characterized as a "therapeutic orphan" (2,4). Consequently, the only definitive treatment remains pregnancy termination and placental delivery, often resulting in preterm birth and complex neonatal outcomes (3,9).

Drug repurposing has emerged as a promising alternative, leveraging the safety profiles of existing medications for new indications (6). Commonly prescribed drugs such as metformin, esomeprazole, and statins show potential to mitigate placental dysfunction and prolong gestation (2,10). These therapies offer hope of transforming the prevention and management of PE (2,7).

Although clinical trials remain the gold standard for validating efficacy (4,7), databases such as ClinicalTrials.gov (11) and the WHO ICTRP (12) reveal a critical research shortage, especially in LMICs, likely due to barriers such as limited infrastructure and funding, which need to be addressed to improve global equity in PE research.

This study maps global inequities in PE drug repurposing research. Following Joanna Briggs Institute (JBI) PCC guidance, we addressed the clinical question (13): *What is the global landscape of interventional clinical trials evaluating drug repurposing for preeclampsia (2000–2025)*?

2. Methodology:

2.1 Inclusion criteria

We conducted a scoping review and landscape analysis of clinical trial registries from the ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) databases, covering the period from January 1, 2000, to December 31, 2025 (14). Inclusion criteria are described in *Table 1*.

Category	Inclusion criteria
Population	Pregnant patients at risk of or diagnosed with preeclampsia (PE) or hypertensive disorders of pregnancy.
Concept	Interventional clinical trials evaluating the repurposing of non-standard pharmacological agents (metformin, statins, esomeprazole, sildenafil, hydroxychloroquine, and melatonin) for the prevention or treatment of preeclampsia.
Context	Global clinical trial registries, specifically ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), include data on country, income level (World Bank), and Maternal Mortality Ratio (MMR).
Study design	Interventional clinical trials evaluating pharmacological efficacy and safety.
Timeline	January 1, 2000, to December 31, 2025.

Table 1. Inclusion criteria

2.2 Systematic search

To capture the broadest possible dataset, the primary search strategy used the condition terms: "Preeclampsia" OR "Pre-eclampsia" OR "Hypertensive Disorders of Pregnancy". Inclusion criteria were restricted to interventional clinical trials evaluating the repurposing of pharmacological agents not currently approved as standard of care for the treatment or prevention of preeclampsia.

Following the initial data retrieval, we systematically screened the intervention fields to identify drug repurposing trials using the following predefined terms: "Pravastatin" OR "statin" OR "Metformin" OR "Esomeprazole" OR "Omeprazole" OR "Proton pump inhibitor" OR "Sildenafil" OR "Tadalafil" OR "Melatonin" OR "Hydroxychloroquine" OR "repurposing" OR "repurposed". Trials evaluating standard prophylactic or therapeutic management (e.g., low-dose aspirin, magnesium sulfate, classical antihypertensives) and non-pharmacological interventions were excluded. In addition, we use the World Bank country's macroeconomic indicators database (January 1 st, 2000 to December 31 st, 2025) (15).

2.3 Data charting

Data charting was performed using a standardized form specifically developed by the research team to capture the diverse variables inherent in drug repurposing research. Following the JBI methodology for scoping reviews, the form was pilot-tested on a random sample of five studies to ensure reliability and consistency across reviewers. Data were extracted from the ICTRP and clinicaltrials.gov and exported to an Excel spreadsheet by one researcher (SA). All records were quality-checked by a second researcher (JT).

The charting process focused on the PCC framework and included: (1) study characteristics (design and country); (2) population details; (3) pharmacological concept (repurposed agent, dosage, and mechanism of action); (4) clinical outcomes; and (5) contextual factors (macroeconomic indicators, MMR, and funding sources). To ensure data integrity, two researchers independently charted the data, with any discrepancies resolved through consensus or consultation with a third senior reviewer.

2.4 Data analyses

To assess the relationship between disease burden and research intensity, Spearman's rank correlation coefficient was calculated between the national MMR and the number of trials conducted in each country. Spearman's test was selected due to the non-parametric distribution of the data. A p-value < 0.05 was considered statistically significant. To ensure the robustness of our findings and to account for potential zero inflation, we performed sensitivity analyses by

repeating the correlation analysis: first, including only countries with at least one trial, and second, restricting the analysis to countries with two or more trials. These analyses aimed to determine if countries with no leading research activity drove the observed lack of alignment. Data analyses were performed in R Studio.

3. Results:

3.1 Study selection and identification

A total of 2,203 clinical trials related to preeclampsia were initially identified through a comprehensive search of global databases: 893 records from ClinicalTrials.gov and 1,310 from ICTRP. After applying specific search filters focused on pharmacological interventions and drug repurposing, the pool was narrowed to 67 clinical trials.

3.2 Screening and eligibility

The 67 records underwent a rigorous manual review to ensure they met the inclusion criteria. During this phase, 20 trials were excluded. The primary reason for exclusion was record duplication across databases (n=20), and the study did not evaluate preeclampsia as a primary condition or focus on standard prophylactic care rather than drug repurposing (n=3).

3.3 Final inclusion

47 trials were included in the final analysis. These trials represent the core evidence base for this study, illustrating the current global landscape of repurposing existing pharmacological agents for the prevention and treatment of preeclampsia *Figure 1*.



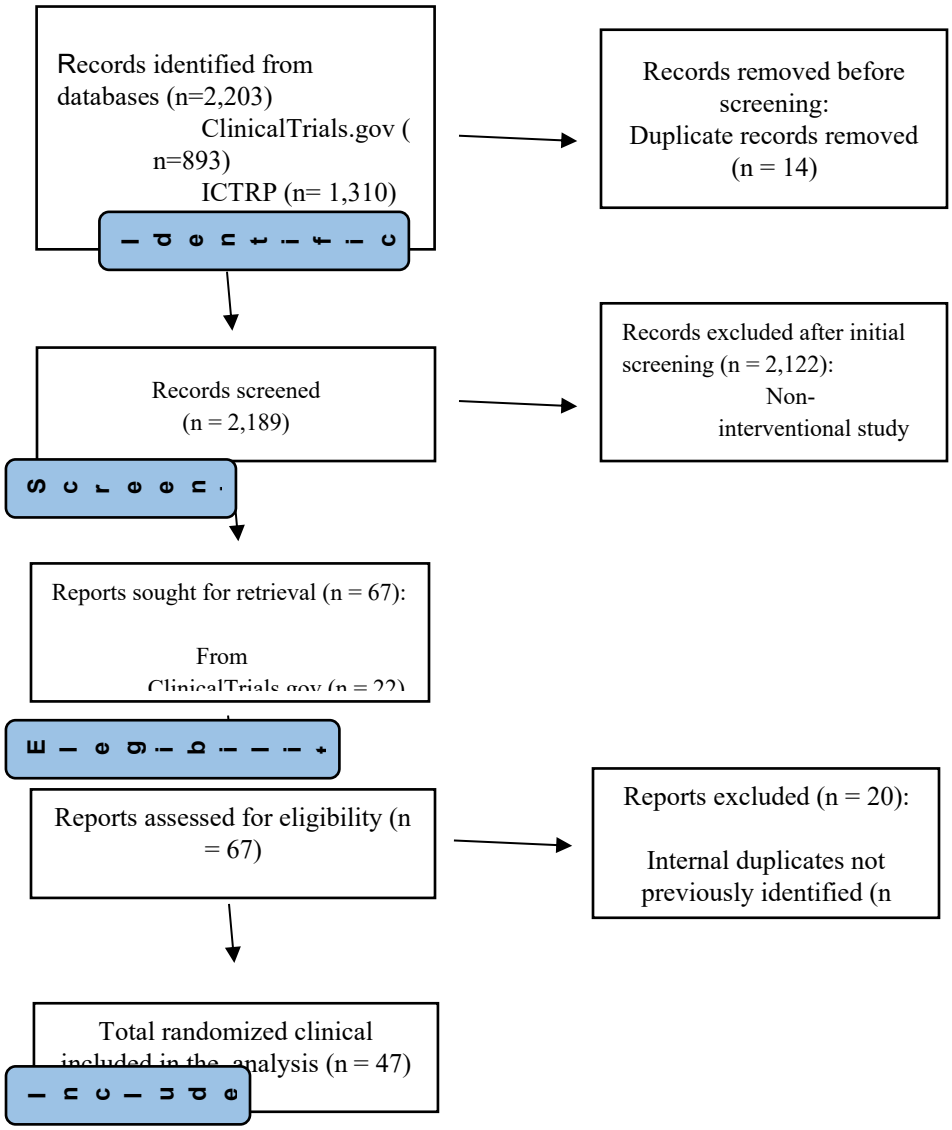


Figure 1. PRISMA flowchart.

3.4 Statistical analyses

Spearman's rank correlation showed no significant relationship between the number of clinical trials and GDP (r_s = 0.40, p = 0.06), *Figure 2A*. Similarly, no significant correlation was found between MMR and the number of clinical trials (r_s = 0.21, p = 0.33); see *Figure 2B.*

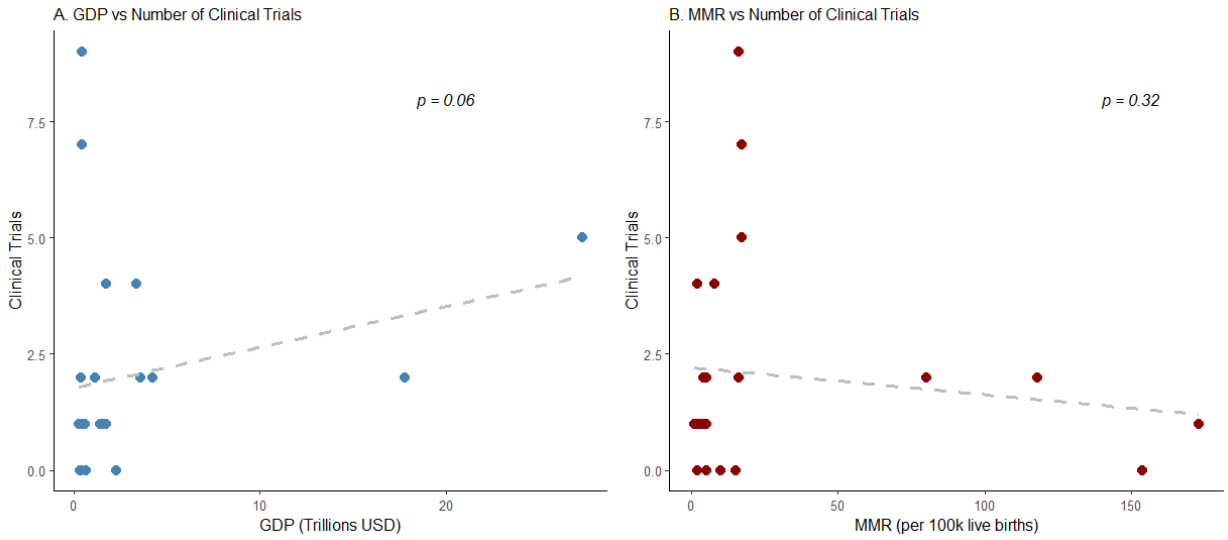


Figure 2. Global correlation analysis of research activity in preeclampsia. A. GDP vs. Number of clinical trials: Spearman's rank correlation between National Gross Domestic Product (GDP) in trillions of USD and the number of clinical trials led per country (rs = 0.40; p = 0.06). B.MMR vs. Number of clinical trials: Spearman's rank correlation between the MMR per 100,000 live births and the number of clinical trials led (rs = 0.21; p = 0.33).

The Spearman correlation between MMR and number of leading trials, restricted to countries with ≥1 leading trial, was rs = 0.43 (p = 0.073), while analysis limited to countries with ≥2 leading trials yielded rs = 0.01 (p = 0.97). All correlations remained non-significant, indicating that the observed mismatch between research leadership and disease burden persisted regardless of zero-inflation.

4. Discussion:

4.1 Background

PE is a multisystemic complication of pregnancy characterized by the onset of high blood pressure and organ damage, whose fundamental pathogenesis resides in underlying placental dysfunction (16). A fundamental pathogenic driver of this syndrome is the disproportionate placental release of the protein soluble fms-like tyrosine kinase-1 (sFlt-1) into the maternal bloodstream. This protein effectively reduces the availability of placental growth factor (PlGF) while simultaneously elevating endothelin-1 (ET-1) levels, thereby triggering systemic endothelial dysfunction characteristic of the disease (17). In this context, drug repurposing has emerged as a therapeutic option for its ability to enhance endothelial function and mitigate inflammation (18). Evidence from animal models suggests a possible role in inhibiting the release of antiangiogenic proteins.

4.1.1 Pharmacological mechanisms

Proton pump inhibitors (PPIs) and metformin have demonstrated, in preclinical studies, their ability to reduce the secretion of antiangiogenic factors and to rescue endothelial function (19). Statins exert various pleiotropic effects, including regulation of nitric oxide (NO) production, reduction of antiangiogenic factors such as sFlt-1, and a notable decrease in both systemic inflammation and oxidative stress (20). Melatonin acts as a potent antioxidant and cytoprotective agent, addressing placental dysfunction (21). In preeclampsia, the placenta releases toxic extracellular vesicles (EVs) and soluble factors that cause systemic endothelial damage in the mother (22). Melatonin significantly reduces the extrusion of these toxic EVs and proinflammatory cytokines from preeclamptic placentae (22). Phosphodiesterase-5 inhibitors (PDE5i) have emerged as a promising drug repurposing strategy for managing placental insufficiency (23). Their primary mechanism is to inhibit cGMP degradation, thereby increasing NO bioavailability and promoting vasodilation of maternal spiral arteries (24). Preclinical evidence indicates that sildenafil reduces uterine artery vascular resistance, thereby improving uteroplacental blood flow (25). These findings led to the formation of international consortia, such as STRIDER, to evaluate the clinical efficacy of sildenafil in severe fetal growth restriction (26). Ongoing research into transplacental transfer and newer molecules such as tadalafil continues to expand the therapeutic potential of PDE5i in obstetrics (25-26). Hydroxychloroquine (HCQ) is a common drug used to treat systemic lupus erythematosus (SLE)

and malaria (26-28). During pregnancy, it is considered safe and effective. HCQ's primary mechanism is inhibition of endosomal toll-like receptors (TLR-7 and TLR-9), thereby significantly reducing the production of pro-inflammatory cytokines (29-30). HCQ promotes a pro-angiogenic state by enhancing the expression of PlGF and decreasing the release of sFlt-1 from the syncytiotrophoblast (31)

4.2 Pharmacological landscape

Metformin was the most frequently evaluated pharmacological agent, included in 31.9% of trials (n = 15). Other prominent interventions were pravastatin and rosuvastatin (n = 11; 23.4%) and esomeprazole (n = 9; 19.1%). Less frequently assessed agents included sildenafil, hydroxychloroquine, and melatonin *Figure 3*.

In terms of clinical purpose, the trials were relatively balanced, with 26 studies (55.3%) targeting the treatment of preeclampsia and 21 studies (44.7%) focusing on prevention. Regarding the financial support, the vast majority of the research was funded by public entities (n = 42; 89.4%), with only a small fraction supported by private organizations (n = 3; 6.4%) or the pharmaceutical industry (n = 2; 4.2%). At the time of this analysis, the majority of trials had not yet reported results, indicating a substantial delay in the dissemination of evidence on these repurposed therapies.

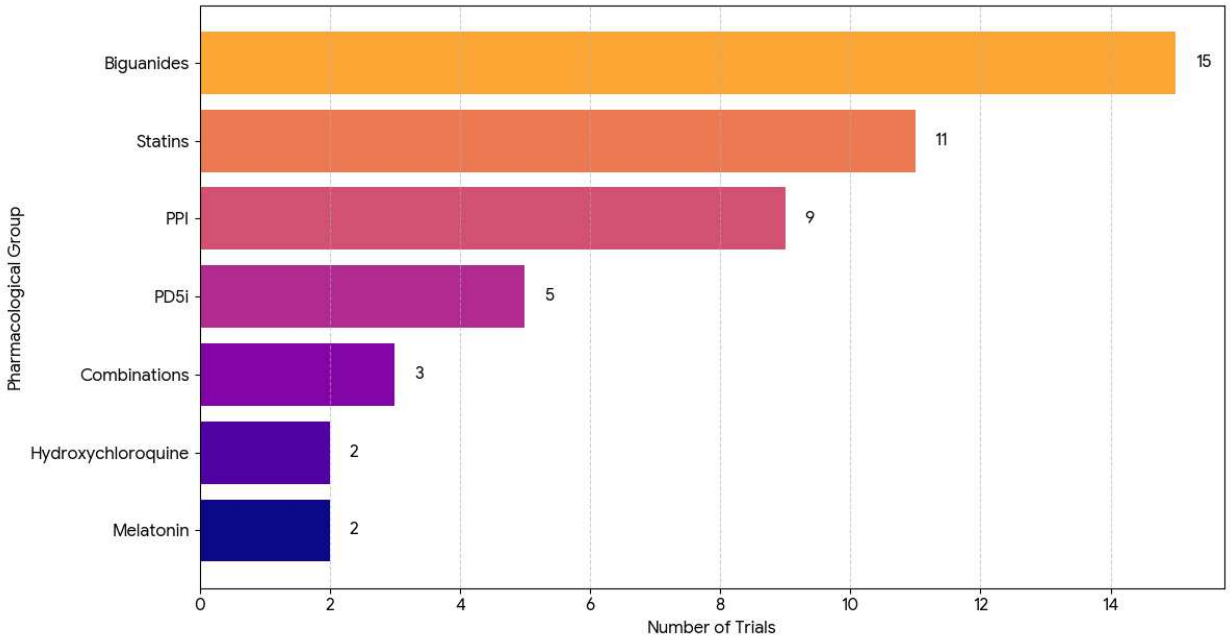


Figure 3. Pharmacological landscape of drug repurposing in pre-eclampsia.Combinations: Metformin and Esomeprazole(n=2); Esomeprazole and Sildenafil (n=1). Source: clinicaltrials.gov and ICTRP databases.

4.3 Global distribution

The global distribution of research activity revealed a profound mismatch between disease burden and clinical investigation. HIC hosted the majority of trials (n = 24; 51.1%), despite reporting the lowest MMR, ranging from 1 to 17 per 100,000 live births *Table 2*. In contrast, LMIC contributed a substantial proportion of research activity (n = 10; 21.3%), whereas upper-middle-income countries (UMIC) accounted for a comparatively smaller share (n = 13; 27.6%), *Figure 4*.

Country	Number of leading trials	Income group	MMR	Drug group
Iran	9	Upper middle income	16	Metformin, sildenafil, melatonin, esomeprazole

Egypt	7	Lower-middle income	17	Esomeprazole, metformin, sildenafil, hydroxychloroquine
USA	5	High income	17	Metformin, esomeprazole, sildenafil, pravastatin,
United Kingdom	4	High income	8	Pravastatin, sildenafil, esomeprazole
Australia	4	High income	2	Esomeprazole, pravastatin, melatonin
Netherlands	2	High income	4	Metformin, omeprazole
India	2	Lower middle income	80	Metformin
South Africa	2	Upper middle income	118	Esomeprazole, metformin
Japan	2	High income	5	Tadalafil, pravastatin
China	2	Upper middle income	16	Metformin, omeprazole
Spain	1	High income	3	Pravastatin
Sweden	1	High income	4	Metformin
Greece	1	High income	5	Pravastatin
Norway	1	High income	1	Pravastatin

Qatar	1	High income	4	Pravastatin
Israel	1	High income	2	Rosuvastatin
South Korea	1	High income	4	Esomeprazole
Indonesia	1	Upper-middle income	173	Pravastatin
Belgium	0	High income	5	Pravastatin
Pakistan	0	Lower middle income	155	Esomeprazole
Chile	0	Upper middle income	22	Esomeprazole
Romania	0	High income	12	Pravastatin
Italy	0	High income	6	Pravastatin

Table 2. Ecological analysis of repurposed pharmacological interventions for preeclampsia: distribution of leading clinical trials by country income level and disease burden source: clinicaltrials.gov and ICTRP databases. Countries with zero trials listed as lead investigators were included in the analysis as collaborative sites.

A prominent leadership role was observed in Iran, which contributed 19.1% (n = 9) of all trials, followed by Egypt, which accounted for 14.9% (n = 7). These findings highlight a concentrated effort in specific middle-income countries to evaluate affordable therapies such as metformin, esomeprazole, and sildenafil, surpassing the individual research volume of HIC leaders such as the United States (n = 5).

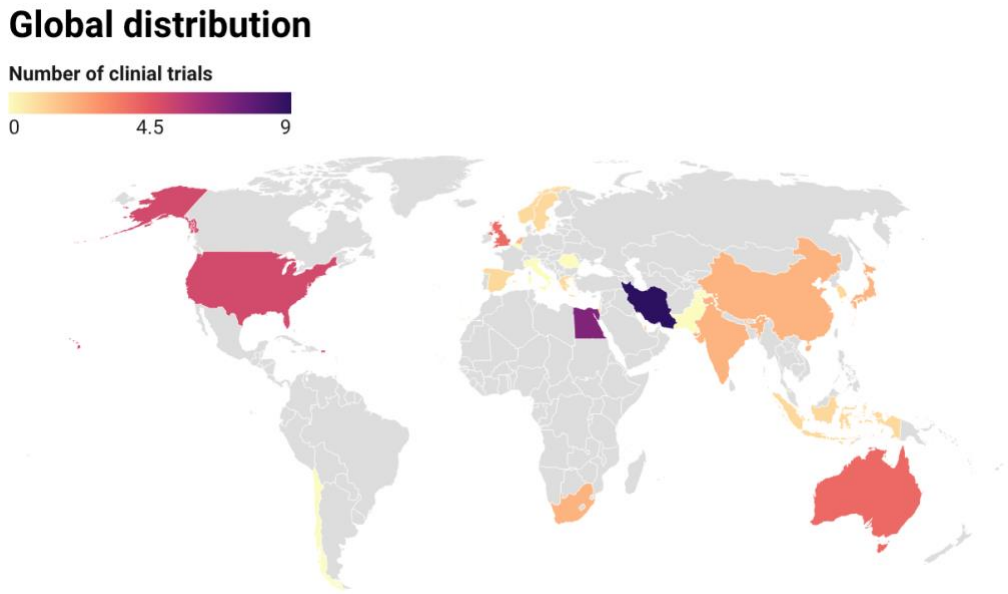


Figure 4. Global distribution clinical trials in drug repurposing for preclampsia [2000 - 2025] Source: clinicaltrials.gov and ICTRP databases. Created with Datawrapper.

Regions with the highest MMR, such as South Africa (MMR: 118) and India (MMR: 80), accounted for only 4.2% (n = 2) each of the global trials. Furthermore, 93.6% (n = 44) of trials were funded by public entities, whereas only 6.38% (n = 3) were sponsored by industry or private institutions. This funding pattern confirms that preeclampsia remains a "therapeutic orphan," highlighting the lack of commercial interest in developing affordable treatments and the heavy reliance on academic and governmental support to advance drug repurposing.

5. Conclusion:

This scoping review and landscape analysis of 47 clinical trials confirms that while drug repurposing offers a promising pathway for preeclampsia, the research architecture is defined by a profound and systemic geographic imbalance. Despite identifying metformin, sildenafil, and esomeprazole as the most studied agents, the overwhelming majority of trials (51.1%) are hosted in high-income countries, which paradoxically report the lowest MMR. Our statistical analysis revealed a critical mismatch, as research activity showed no significant correlation with either national wealth or clinical burden. Notably, leadership in this field is driven by middle-income nations such as Iran and Egypt, which surpass the research volume of global powers such as the

United States despite limited commercial interest, as evidenced by the fact that 89.4% of trials rely on public or academic funding.

6. Limitations:

This study is primarily limited by its reliance on ClinicalTrials.gov and WHO ICTRP registries, which may exclude local or non-registered pilot studies, potentially underestimating research activity in some regions. Additionally, a significant reporting lag was observed, as many trials lacked updated status or published results, hindering the assessment of clinical outcomes. The ecological design using national GDP and MMR indicators provides a global landscape but may overlook internal disparities within countries. Finally, by focusing exclusively on drug repurposing, this review does not account for the total volume of preeclampsia research involving basic science, diagnostics, or non-pharmacological interventions.

7. Protocol registration

A detailed protocol for this scoping review was registered with the Open Science Framework (OSF) and is available at (URL: https://osf.io/vf3hu/). The registration was completed after data extraction but before manuscript submission, ensuring transparency and adherence to the methodological standards for scoping reviews.

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The authors declare that they did not receive funding for the research.

Competing interests

The authors declare no competing interests

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Adriana Calzada, my grandmother, who passed away on December/24/2024

Ethics approval

Not required, analysis of publicly available registry data.

Availability of data

Search syntax is available at https://osf.io/vf3hu. Data are available on ClinicalTrials.gov and ICTRP websites.

Declaration of generative AI use

The authors declared that they did not use artificial intelligence-assisted technologies (such as large language models, chatbots, or image creators) in the production of this work.

CRediT author statement

Sergio David Angulo: Conceptualization, Data curation, Formal analysis, Investigation ,Methodology, Project administration, Resources, Software, Supervision , Validation ,Visualization, Writing , Original draft Writing ,Review and Editing. **Sandra Olaya**: Conceptualization, Data curation ,Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, **Juan Diego Trujillo**: Data curation ,Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision Julián David Toro:Investigation, Methodology, Project administration, Resources, Software, Supervision . **Isabella Montealegre:** Resources, Software, Supervision , Validation ,Visualization, Writing , Original draft Writing ,Review and Editing. **Tatiana Perdomo**:Conceptualization, Data curation, Formal analysis, Investigation ,Methodology, Project administration, Resources, **Samy Giraldo**: Writing , Original draft Writing ,Review and Editing, **Silvana Castaño**:Validation ,Visualization, Writing , Original draft Writing ,Review and Editing **Isabella Vidal**: Validation ,Visualization, Writing , Original draft Writing ,Review and Editing

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