Global Innovator's Briefing: Rare Diseases

Preeclampsia

Are you aware of it?

Preeclampsia (PE)

- A systemic hypertensive condition unique to pregnancy
- Occurs as a result of factors released by the placenta
- Manifests as early-onset (<34 weeks of gestation) or late onset (>34 weeks of gestation)
- Has a mild and a severe form (that requires immediate hospitalisation for acute or intensive care)
- Can develop into eclampsia, in which seizures and/or coma simultaneously occur
- Responsible for > 70,000 maternal deaths a year (1 maternal death, every 7.5 minutes because of PE), globally
- Persists post-delivery and can create significant and long-lasting multi-organ damage in the mother
- Post-delivery (postpartum), the neonate is at high risk of long-term multi-tissue morbidity

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Points in this briefing that may be of interest for the innovator

- *Issues of bias and disparity in healthcare*
- *The benefits of a 'Policy to Practice' integrated stakeholder ecosystem to innovation in rare diseases*
- *Focusing solutions on LMIC: direct development or repositioning*
- *Experiences in design, and roll-out of innovations in low resource settings*
- *Evidence generation and evaluation in low resource settings*
- *How innovations designed for LMIC can have global impact*

About Echino Innovator Briefings: Rare Diseases,

These briefings are designed as introductions for **early-stage innovators, covering a range of diverse rare diseases**. They are based upon freely available peer reviewed and referenced or professional information, that have been designed as a 'cog' between the two worlds of healthcare need and innovation implementation. Four are planned: some core sections will be identical throughout.

To stimulate or aid the innovator in any global geography, these introduce the state-of-the-art. the stakeholders and their interactions to anyone or any entity that is interested in innovating a solution (interventional, diagnostic, med tech, med device, digital health, healthcare process, occupational and physical therapy, patient support globalisation) for a Rare Disease, whether its social entrepreneurship, charitable or for-profit.

Why Innovator focused specific communication:
There is a knowledge gap with specific relevance to Rare Diseases between innovators and the stakeholder communities that play a pivotal and critical role in making sure innovations deliver real benefit, that has greater pertinence than more frequent diseases due to patient numbers and product development costs. It can be baffling to know where to start.

I have participated in sufficient investment committee review meetings with presentations focusing on rare diseases, often with a feeling of that only one or two stakeholders or issues have been truly considered: this makes the transition of the idea to a beneficial product or solution much more difficult.

Inversely, for an innovator to identify and understand the spectrum of knowledge needed is daunting: a significant amount of the information is very technical in content, with a broad spread across many sources and often focused on the authors immediate communities.

I have not tried to simplify the knowledge (except when it is very clinical terminology, specifically on symptoms), and always provided references. References are provided according to the schedule of people who work in innovation, where possible next to the pertinent information being discussed. For purposes of brevity, I have only indicated the first author et al, in most cases with the link (mainly to PubMed). I know this not the normal standard, but this is tailored for the audience.

References are not designed to favour any given stakeholder or KOL, nor are they are substitutes for digging much deeper if the innovator is serious. If, any KOL has felt they have been left out, this was not the intention (apologies): many more publications were read than referenced (the ones indicated by the book symbol are *suggested introductory starting points and are technical/specialised in most cases*).

The briefings were started over summer 2022, with the aim to be globally focused and comprehensive… and like all knowledge exploration exercises, the more you discover the more you realise you don't know... so they are not necessarily brief.

They do not include any specific references to standards or regulations applied in the different geographies for product development, manufacture and validation... for the innovator, this information is widely available and for you to find. They also do not include market valuations: there is sufficient information present in these briefs including the supplementary material of the references, plus easily available online price catalogues for you to do the calculation yourself. They are not competitive intelligence reports: company organisations, clinical trial databases and stock exchange company listings are good starting points to identify other commercial endeavours.

Sometimes only specific stakeholders and single geographies are prioritised with a focus on bottom-line returns, this is somewhat understandable but as a general principle Rare Disease focused work is a long-haul and avoiding care disparity is a major goal. This may require a global approach to innovation in solution pricing, and reflection on strategies related to the orphan drug legislation and designation, to make sure investment is not diluted too much on competing too-similar initiatives. A forward movement without balance between all stakeholders is a movement backwards.

Many patients with all types of rare diseases, and their caregivers have stepped up and got involved, knowing full well that their involvement will likely not generate a benefit for them in their lifetime or for the ones they care for, but may help the next generation. I don't think very many of them made that decision with another entities financial ROI as their main objective.

What these are not:
They are unfortunately not multilingual: I only had the time to write them in English. If anyone is interested in generating multilingual/multicultural sensitive versions, please reach out and I am happy to provide the original word doc. for translation.

These are **not adverts**: i.e., after reading, if stimulated, following further detailed reading that is needed first: the innovators next point of contact should be a KOL: Patient Association or a Medical Professional/Researcher.

Declaration:
I have no conflict of interest with any entity (public or private), I represent no faith or faith associated body, I represent no political view or political body, I represent nor am paid by any entity: non-profit, pharmaceutical or biotech, for these briefings.

And I am enormously grateful to the vast array of open-source publications, and authors, databases, charities, associations and NGOs that are making the knowledge and information for these long briefings freely available.

Jonathan Dando PhD

cite: Dando JS. Preeclampsia: Rare Disease Innovators Briefing: Last updated Nov 2022.
Accessed from: www.echino.eu/knowledge

Section 1: Preeclampsia: Global annual incidence

An estimated 70,000 maternal deaths occur every year from PE

Rana S, et al. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019;124(7):1094-1112. **Link**: https://pubmed.ncbi.nlm.nih.gov/30920918/

Table 1: 2021 estimated incidence ranges and numbers of PE in pregnancy (calculation sources explained below)

Location	Number of births by region*	Incidence - low range (%)	Number - low range	Incidence - high range (%)	Number - high range
Africa	45,368,652	0.5	226,843	2.3	1,043,478
Asia	67,226,688	0.2	134,453	6.7	4,504,188
Europe	6,879,818	2.8	192,634	5.2	357,750
Latin America	9,708,710	1.8	174,756	7.7	747,570
North America	4,097,901	3.0	106,545	4.0%	163,916
Oceania	692,927	2.8	19,401	9.20%	63,749
Total global	133,974,696		854,632		6,880,651

Overarching global PE prevalence estimates are at 4.6% of all pregnancies = 6,521,744 (biases towards higher range)

The start of the patients' journey and PE risk factors

The Woman discovers She is pregnant

↓

The Woman decides whether She would like to continue with the pregnancy

↓

The Woman enters antenatal care pathway

↓

WHO and generally applied guidelines for good care. At least 8 antenatal visits before delivery: the first one typically at the end of **12 weeks** (The first trimester)

↓

Depending on infrastructure and need, visits can happen at mobile clinics, community care centres, family doctor's office or the hospital (outpatient)

↓

UNLESS

The Mother is considered **at risk**, **correctly identified and diagnosed** then the need for antenatal visits can be from 15 visits upwards, or hospitalisation

Moderate PE risk factors

- First pregnancy (also termed nullparity)
- Pregnancy involves twins or triplets
- Age >35 or 40 years of age (guideline specific)
- >10 years since the previous pregnancy
- BMI >30 or 35 (guideline specific)
- Family history of PE
- IVF as method of conception
- Social determinants of health (health inequity*)

Severe PE risk factors

- Combination of two or more of the above
- Kidney disease
- Type 1 or Type 2 diabetes
- Chronic hypertension
- Concomitant autoimmune diseases
- Hypertensive in previous pregnancy

Eclampsia risk factors

- The above
  plus
- Neurosensory symptoms: headaches and overresponsive reflexes (hyperreflexia)

Source of epidemiology calculation:

*Annual number of births https://ourworldindata.org/grapher/annual-number-of-births-by-world-region?tab=table
(This was the closest possible accurate source and estimation of pregnancies that could be obtained and used).

+*Epidemiology of PE:* Mou, A.D., Barman, Z., Hasan, M. *et al.* Prevalence of preeclampsia and the associated risk factors among pregnant women in Bangladesh. *Sci Rep* **11**, 21339 (2021). **Link** https://www.nature.com/articles/s41598-021-00839-w

Global definitions of rare disease as a function of frequency (link also has Orphan drug legislation by country):

Schouten A, KEI Briefing Note 2020:4 Selected Government Definitions of Orphan or Rare Diseases. Revised October 28, 2020. Accessed, October 2022 from https://www.keionline.org/bn-2020-4

Whether a disease is classified as rare varies between geographies: for example, if it has a general population prevalence of ≤1 patient per 2,000 people in the EU, impacts ≤200,000 people in the USA, or ≤1 person per 2,500 people in Japan, it is considered rare.

PE occurs at an average of **0.76 cases per 2000** people with an estimated global average incidence of 4.6% of all pregnancies.

Hahn S. Preeclampsia - will orphan drug status facilitate innovative biological therapies? Front Surg. 2015;2:7. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4341571/

von Dadelszen, et al. Management of Preeclampsia in Low- and Middle-Income Countries: Lessons to Date, and Questions Arising, from the PRE-EMPT and Related Initiatives. Maternal-Fetal Medicine: April 2021 - Volume 3 - Issue 2 - p 136-150 **Link:** https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

*Updated ACOG and SMFM Recommendation: Low-Dose Aspirin Use for the Prevention of Preeclampsia and Related Morbidity and Mortality. December 2021. American College of Obstetricians and Gynecologists. Accessed November 2022 from: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/12/low-dose-aspirin-use-for-the-prevention-of-preeclampsia-and-related-morbidity-and-mortality#.

Section 2: Gender healthcare disparity and its impact in PE.

Gender disparity in healthcare is still prevalent. For a rare disease that only impacts the gender towards which most disparity occurs this contradicts one of the core concepts of orphan drug designation: a regulation that makes innovator motivation and capital investors involvement in rare disease innovation more attractive.

'Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients'

European Parliament and Council of the European Union. Regulation (EC) NO 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan medicinal products.

'Gender, understood as "social relationships between males and females in terms of their roles, behaviours, activities, attributes and opportunities, and which are based on different levels of power", is one of the main social determinants of health. The damage caused to population health by gender inequality across the globe is immense and justifies comprehensive actions addressing gender equity in health at all levels.'

Alcalde-Rubio, L., *et al.* Gender disparities in clinical practice: are there any solutions? Scoping review of interventions to overcome or reduce gender bias in clinical practice. *Int J Equity Health* 19, 166 (2020). Link: https://pubmed.ncbi.nlm.nih.gov/32962719/

*'Preeclampsia is associated with a 4-fold increase in future incident heart failure and a 2-fold increased risk in coronary heart disease, stroke, and death because of coronary heart or cardiovascular disease. Our study highlights the importance of lifelong monitoring of cardiovascular risk factors in women with a history of preeclampsia.'**

Wu P, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2). **Link:** https://pubmed.ncbi.nlm.nih.gov/28228456/

**CVD is not the only significant morbidity that co-manifests with PE (covered in 'symptoms').*

'Cardiovascular disease is the leading cause of death in women. Decades of grassroots campaigns have helped to raise awareness about the impact of cardiovascular disease in women, and positive changes affecting women and their health have gained momentum. Despite these efforts, there has been stagnation in the overall reduction of cardiovascular disease burden for women in the past decade. Cardiovascular disease in women remains understudied, under-recognised, underdiagnosed, and undertreated.'

Vogel B et el. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. The Lancet, Vol. 397, No. 10292, 2021. **Link:** https://www.thelancet.com/infographics-do/women-and-cardiovascular-disease

Gender disparity in mobile technology usage

Digital health solutions and their developers should verse themselves with the GMSA publication on the gender gap in mobile usage in LMIC countries with regard to all steps of the innovation process. 912 million adult women in LMIC do not use mobile internet, with the top three barriers for both mobile ownership and usage being affordability, digital literacy and safety/security (considering health data privacy regulations this is significant).

Link: https://www.gsma.com/mobilefordevelopment/blog/the-mobile-gender-gap-report-2022/

If integrated into world demographics, (with definition of an adult women as 15-years and older to account for cultural differences) the implication is over a third of adult women in LMIC do not use mobile internet.

More detailed information related to mobile technology is addressed in the healthcare infrastructure availability section of the briefing, including links to coverage maps, reports on data connectivity quality and availability, case studies and a global guide.

When compounding factors that influence healthcare provision exist, these need to be integrated into the innovation design process, including:

- Evidence generation: where and how?
- Patient population involvement: do they know, can they be reached?
- Complete population awareness of the indication: are all pertinent parties informed and involved?
- Product awareness: do they know it exists?
- Product prescription: can they use it?
- Capacity for product usage: is it easy to use?
- Product pricing: can they afford it?

Section 3: What are the symptoms of PE and how heterogenous are they

Table 2: Non-exhaustive list of the symptoms experienced by patients diagnosed with PE prepartum.

Frequency (%)	Description
80–99	Proteinuria Hypertension Elevated systolic blood pressure Elevated diastolic blood pressure Abnormality of the placenta
5–29	Abnormality of the kidney Abnormality of vision Abnormality of the nervous system Intrauterine growth retardation Abdominal pain Headache Elevated hepatic transaminase Abnormality of the hepatic vasculature Increased body mass index
1–<4	Polycystic ovaries Thrombocytopenia Acute kidney injury Chronic kidney disease Sleep disturbance Autoimmunity Elevated serum creatinine Heliobacter pylori infection Gestational diabetes

Source of data for table: *Data obtained from Orphanet 'rare diseases: clinical signs and symptoms. For purpose of brevity, symptoms summarised and indicated by organ. The complete list can be found at the original source https://www.orpha.net/consor/cgi-bin/Disease_HPOTerms.php?lng=EN with a detailed explanation of the data.*

Ives C, et al. Preeclampsia—Pathophysiology and Clinical Presentations. *J Am Coll Cardiol.* 2020, 76 (14) 1690–1702.
Link: https://pubmed.ncbi.nlm.nih.gov/33004135/

Erez O, et al. Preeclampsia and eclampsia: the conceptual evolution of a syndrome. Am J Obstet Gynecol. 2022;226(2S):S786-S803.**Link:** https://pubmed.ncbi.nlm.nih.gov/35177220/

Immediate and long-term postpartum symptoms that have been reported

For the mother

Immediate:
- Postpartum depression
- Postpartum psychosis
- Thrombocytopenia
- Haemorrhage
- Low blood platelet count

Long-term risk increase:
- Cardiovascular diseases
- Stroke
- Chronic hypertension
- Venous thromboembolism

For the infant

Immediate:
- Low birth weight
- Breathing irregularities while sleeping
- Respiratory stress syndrome
- Perinatal stroke
- Neurodevelopment disorders

Long-term risk increase:
- Autism spectrum disorder/ADHD
- Cognitive impairment
- Schizophrenia
- Cardiovascular diseases
- Epilepsy

Lu HQ, Hu R. Lasting Effects of Intrauterine Exposure to Preeclampsia on Offspring and the Underlying Mechanism. AJP Rep. 2019 Jul;9(3):e275-e291.**Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6736667/

Brown MA, et al. Recognizing Cardiovascular Risk After Preeclampsia: The P4 Study. J Am Heart Assoc. 2020 Nov 17;9(22):e018604. **Link:** https://pubmed.ncbi.nlm.nih.gov/33170079/

Mbarak, B., et al. Postpartum depression among women with pre-eclampsia and eclampsia in Tanzania; a call for integrative intervention. BMC Pregnancy Childbirth 19, 270 (2019). **Link:** https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-019-2395-3

Seely EW, et al. Cardiovascular Health After Preeclampsia: Patient and Provider Perspective. J Womens Health (Larchmt). 2021 Mar;30(3):305-313. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8020553/

Haßdenteufel, K., et al. Long-term effects of preeclampsia on maternal cardiovascular health and postpartum utilization of primary care: an observational claims data study. Arch Gynecol Obstet (2022). **Link:** https://link.springer.com/article/10.1007/s00404-022-06561-w

Amaral LM, et al. Preeclampsia: long-term consequences for vascular health. Vasc Health Risk Manag. 2015 Jul 15;11:403-15. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4508084/

Caropreso L, et al. Preeclampsia as a risk factor for postpartum depression and psychosis: a systematic review and meta-analysis. Arch Womens Ment Health. 2020 Aug;23(4):493-505. **Link:** https://pubmed.ncbi.nlm.nih.gov/31802249/

Korzeniewski SJ, et al The Global Pregnancy Collaboration (CoLab) symposium on short- and long-term outcomes in offspring whose mothers had preeclampsia: A scoping review of clinical evidence. Front Med (Lausanne). 2022;9:984291. **Link**: https://pubmed.ncbi.nlm.nih.gov/36111112/

Turbeville HR, Sasser JM. Preeclampsia beyond pregnancy: long-term consequences for mother and child. Am J Physiol Renal Physiol. 2020 Jun 1;318(6):F1315-F1326. **Link:** https://pubmed.ncbi.nlm.nih.gov/32249616/

WIETESKA, Małgorzata, et al. Preeclampsia – long-term effects on mother and child. *Journal of Education, Health and Sport*[online]. 21 August 2021, T. 11, nr 8, s. 261–267. **Link:** https://apcz.umk.pl/JEHS/article/view/JEHS.2021.11.08.027

Ye Y, et al. Preeclampsia and Its Complications Exacerbate Development of Postpartum Depression: A Retrospective Cohort Study. Biomed Res Int. 2021;2021:6641510. **Link:** https://pubmed.ncbi.nlm.nih.gov/33977108/

Section 4: Assessing the impact of PE on the Health-related quality of life (HRQoL):

- Connecting a change in a specific clinical outcome to a change in QoL adds definition to the benefit of the solution, with respect to every possible solution.
- QoL changes applies to the patient and the caregiver.
- Depending on the clinical symptom being targeted and its severity, QoL changes may occur in the short term or over a longer period; or clinical symptom alleviation may not result in an identifiable change in QoL.
- Patient Reported Outcome Measures (PROMs) are designed to measure these. Their complexity can vary between use as *patient monitoring tools* such as in daily patient care, to larger scale multi-dimensional tools used in complex case management and clinical trials.

Introduction to PROMs:

Patient-reported outcome measures (PROMs) as proof of treatment efficacy

Kluzek S, et al. BMJ Evid Based Med. 2022 Jun;27(3):153-155.

Link: https://pubmed.ncbi.nlm.nih.gov/34088713/

To date the only validated patient reported outcomes for PE, that can be used throughout all locations of care and during clinical trials have been generic

Specific PROMs are presently being designed or validated by Healthcare Professionals (HCPs)

Dickinson FM, et al. Assessing quality of care in maternity services in low and middle-income countries: Development of a Maternity Patient Reported Outcome Measure. PLOS Glob Public Health. 2022 2(3): e0000062. **Link:** https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0000062

Depla AL, et al. Patient-Reported Outcome and Experience Measures in Perinatal Care to Guide Clinical Practice: Prospective Observational Study. J Med Internet Res. 2022;24(7):e37725. **Link:** https://pubmed.ncbi.nlm.nih.gov/35787519/

In randomized trials evaluating interventions for pre-eclampsia, critical information related to the primary outcome, including definition and measurement, is regularly omitted. Developing a core outcome set for pre-eclampsia trials would help to inform primary outcome selection and outcome measure reporting.

Duffy JMN, et al; International Collaboration to Harmonize Outcomes for Pre-eclampsia (iHOPE). A systematic review of primary outcomes and outcome measure reporting in randomized trials evaluating treatments for pre-eclampsia. Int J Gynaecol Obstet. 2017;139(3):262-267. **Link:** https://pubmed.ncbi.nlm.nih.gov/28803445/

To date, there is no PROM agreed which would be suitable as patient reported outcome measure for the assessment of the quality of care women receive during pregnancy or after childbirth. However, there are a variety of available assessment tools which could potentially be helpful in developing new and existing PROMs for maternity care.

Dickinson, FM., et al. Patient reported outcome measures for use in pregnancy and childbirth: a systematic review. BMC Pregnancy Childbirth. 2019; 19, 155. **Link:** https://pubmed.ncbi.nlm.nih.gov/31060519/

PROMs identified that had been used included generic, psychological, physical and social or open types measures:

- SF36
- EQ-5D-3 L
- Hyperemesis Impact of Symptoms (HIS)
- Edinburgh Postnatal Depression Scale (EPDS)
- Milligan's postpartum fatigue scale
- PTSD checklist
- 9-item Patient Health Questionnaire (PHQ-9)

Section 5: The 'Voice of the Patient'

Patient Associations work closely with the HCPs and patients to address ways to better understand life with PE through written testimonials of experience and stories - 'the voice of the patient'.

The innovator needs to visit these links to obtain a better understanding of how PE impacts their QoL, as the patient sees and feels it, to understand what their innovation can or should do.

https://action-on-pre-eclampsia.org.uk/experience/

https://www.preeclampsia.org/public/our-stories

+

Tsigas EZ. The Preeclampsia Foundation: the voice and views of the patient and her family. Am J Obstet Gynecol. 2022 ;226(2S):S1254-S1264.e1. Link: https://pubmed.ncbi.nlm.nih.gov/34479720/

There are very few patients voice reports for PE in Low- and Middle-Income Countries (LMIC) or LMIC location specific patient associations (with an identifiable online presence)

Bijl RC, et al. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. BMJ Open. 2022;12(3):e057795. Link: https://pubmed.ncbi.nlm.nih.gov/35241475/

The preeclampsia patient journey. The Preeclampsia Foundation, last updated May 10 2022, accessed November 2022: https://preeclampsia.org/patientjourney

Vásquez, C. L., et al. Hazard, death and sequels: Perception on severe preeclampsia by those who lived it. Enfermería Global, 2014 13(2). Link: https://scielo.isciii.es/pdf/eg/v13n34/en_enfermeria2.pdf

Stern C, Trapp EM, Mautner E, Deutsch M, Lang U, Cervar-Zivkovic M. The impact of severe preeclampsia on maternal quality of life. Qual Life Res. 2014;23(3):1019-26. Link: https://pubmed.ncbi.nlm.nih.gov/24081868/

Hoedjes M, et al. Poor health-related quality of life after severe preeclampsia. Birth. 2011;38(3):246-55. Link: https://pubmed.ncbi.nlm.nih.gov/21884233/

For patients with Preeclampsia, organisations providing support and information are essential: the following represents a (non-exhaustive) list of organisations and bodies.

These types of organisations move mountains. The innovator should take time to explore everything they have done, their outputs and what they continue to do, during their own reflections on the benefits they think they can provide.

Table 3: patient associations, organisations and bodies providing support and information

Name	Location	Geographic focus	Website	Languages
Patient associations				
Preeclampsia foundation	US	US/Global	https://www.preeclampsia.org (also coordinates the preeclampsia registry that can be found at https://www.preeclampsiaregistry.org)	135 different languages and dialects
Action on pre-eclampsia	England	UK/Global	https://action-on-pre-eclampsia.org.uk	English
March of dimes	US	US/Global	https://www.marchofdimes.org	English
STOP Preeclampsia	Spain	Spanish speaking population	https://www.stop-pe.org	Español
European foundation for the care of newborn infants	German	EU	https://www.efcni.org	English
Concept foundation	Switzerland	Global	https://www.conceptfoundation.org	English
Tommy's	UK	UK	https://www.tommys.org/about-us	English
Preeclampsia Research	Unknown	Unknown	https://www.preeclampsiaresearch.com	English
Clinical organisations/networks				
International federation of Gynaecology and obstetrics (FIGO)	UK	global	https://www.figo.org (with network of national based organisations on map)	Spanish/English
Rare Disease organisations				
Orphanet	Europe	Europe/Global	https://www.orpha.net/consor/cgi-bin/index.php	English
Information disseminators and patient advocacy				
Eurordis	Europe	Europe/Global	https://www.eurordis.org	31 different languages
The Lancet	online	online	https://www.thelancet.com/clinical/diseases/pre-eclampsia	English
Nature	online	online	https://www.nature.com/subjects/pre-eclampsia	English
Orphanet Journal of Rare Diseases	online	online	https://ojrd.biomedcentral.com	English
ScienceX	online	online	https://medicalxpress.com/tags/pre-eclampsia/	English

Section 6: HCP care pathways in PE: Policy to practice

PE is one of the few rare diseases that has a proven global policy to practice vertical integration in efforts to optimise health care. There is a two-way flow of information between all entities with very tangible benefit.

Policy bodies

WHO recommendations for
Prevention and treatment of pre-eclampsia and eclampsia

Focuses on overall policy and healthcare requirements globally

Link: https://www.who.int/publications/i/item/9789241548335

International HCP Associations

International Federation of Gynecology and Obstetrics (FIGO):

Poon LC et at. A Pragmatic Guide for First-Trimester Screening and Prevention: Compiled FIGO. Int. J. Gynaecol Obstet. 2019; 145 Suppl 1. Link: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.12802

Poon LC et at. A literature review and best practice advice for second and third trimester risk stratification, monitoring, and management of pre-eclampsia: Compiled by the Pregnancy and Non-Communicable Diseases Committee of FIGO. Int. J. Gynaecol Obstet. 2021; 154 Suppl 1. Link: https://pubmed.ncbi.nlm.nih.gov/34327714/

National recommendations and guidelines (examples)

They also can perform implementation and economic evaluations of new innovations to assess applicability.

Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. *BMJ* 2019;366:l5119. Link: https://www.bmj.com/content/366/bmj.l5119/infographic **Link** (Version en espanol): https://www.bmj.com/content/bmj/suppl/2019/10/29/366.sep09_5.l5119.DC1/hypertension_pregnancy_web_esp_v5.pdf

2020_SFAR et CNGOF_Prise en charge de la patiente avec une pré-éclampsie sévère. **Link**: http://www.cngof.net/Publications-CNGOF/Pratique-clinique/RPC%20COLLEGE/2020/RFE%20pre-eclampsie_2020.pdf

Guía de Asistencia Práctica: Trastornos hipertensivos en la gestación. SOCIEDAD ESPAÑOLA DE GINECOLOGÍA Y OBSTETRICIA (SEGO). Progresos de Obstetricia y Ginecología 2020;63(4): 244-272. **Link**: https://sego.es/documentos/progresos/v63-2020/n4/GAP-Trastornos%20hipertensivos%20gestacion.pdf

German Guidelines on Preeclampsia Management. International Workshop on Prenatal Screening Berlin, 02.06.2018. **Link:** https://www.brahms.de/images/00_downloads/prenatal-screening/PNS_Forum/2018/09-presentation-brahms-pns-forum-2018-Verlohren.pdf

Ministry of Health. 2018. Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in New Zealand: A clinical practice guideline. Wellington: Ministry of Health. **Link**: https://www.health.govt.nz/system/files/documents/publications/diagnosis-and-treatment-of-hypertension-and-pre-eclampsia-in-pregnancy-in-new-zealand-v3.pdf

Implementation guides (examples)

The national recommendations are changed into implementation guides that can be used by the HCPs

Highly recommended for the innovator due to clear algorithms: CMQCC Quality Improvement Toolkit - Improving Health Care Response to Hypertensive disorders in Pregnancy. Available from www.cmqcc.org

Rajagopalan C. et al. Clinical Practice Care Pathway: Maternity services. Eclampsia and Severe Pre-eclampsia Yorkshire Protocol. The Mid Yorkshire Hospitals NHS Trust. Version 5b, November 2019. Accessed from: https://www.oaa-anaes.ac.uk/assets/_managed/cms/files/Clinical%20Guidelines/Eclampsia%20Severe%20Preeclampsia%20v5b.pdf

The women's: the royal women's hospital Victoria, Australia. Guideline. Pre-eclampsia management. **Link:** https://thewomens.r.worldssl.net/images/uploads/downloadable-records/clinical-guidelines/pre-eclampsia-management_280720.pdf

Reports and case studies on Use, Adaptation and Evaluation, then inform the unmet need

von Dadelszen P, et al. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. Lancet. 2020;396(10250):553-563. **Link:** https://pubmed.ncbi.nlm.nih.gov/32828187/

Perez-Cuevas R, et al. Critical pathways for the management of preeclampsia and severe preeclampsia in institutionalised health care settings. BMC Pregnancy Childbirth. 2003;3(1):6. **Link:** https://pubmed.ncbi.nlm.nih.gov/14525621/

Bijl RC, et al. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. BMJ Open. 2022;12(3):e057795. **Link:** https://pubmed.ncbi.nlm.nih.gov/35241475/

Warren, C.E., et al. A primary health care model for managing pre-eclampsia and eclampsia in low- and middle- income countries. Reprod Health 17, 46 (2020). **Link:** https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-020-0897-0

von Dadelszen, et al. Management of Preeclampsia in Low- and Middle-Income Countries: Lessons to Date, and Questions Arising, from the PRE-EMPT and Related Initiatives. Maternal-Fetal Medicine: 2021 - Volume 3 - Issue 2 - p 136-150. **Link:** https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

Lazo-Vega L, et al. ACOG and local diagnostic criteria for hypertensive disorders of pregnancy (HDP) in La Paz-El Alto, Bolivia: A retrospective case-control study, The Lancet Regional Health - Americas, Volume 9, 2022, 100194. **Link:** https://www.thelancet.com/action/showPdf?pii=S2667-193X%2822%2900011-4

There are still some bottlenecks in LMIC adherence to recommended processes, but this level of integration across the HCP stakeholders permits innovators to design targeted solutions that can alleviate investors' concerns

Section 7: Global healthcare infrastructure availability (personnel and beds)

'It must be recognized that the majority of pregnancies globally are not supervised by experts (ie, midwives, obstetricians, or family doctors with specific postgraduate certification in obstetrics) either antenatally, during birth, or postnatally.'

von Dadelszen, et al. **Link:** https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

Table 4: Estimated Healthcare personnel per 10,000 total population
(*Except for Midwives that are 'numbers per 10,000 women aged 14–49 years')

Region	Medical doctors (Family doctors excluded)	Family doctors (GPs)	Nurses	Community Health Workers	Midwives*
Africa	1.21	2.19	11.29	3.66	7.02
Asia	10.61	3.26	26.24	6.05	12.9
Europe	33.41	9.10	90.83	Not available	9.3
Latin America	24.97	9.87	60.20	6.91	4.62
North America	17.58	7.86	149.44	Not available	1.31
Western Pacific	21.81	7.95	89.63	Not available	12.3

Source: The 2022 update, Global Health Workforce Statistics World Health Organisation, Geneva.
Medical and Pathology lab staff, physiotherapy personnel and community health worker total number statistics available by country level only.
See: https://www.who.int/data/gho/data/themes/topics/health-workforce

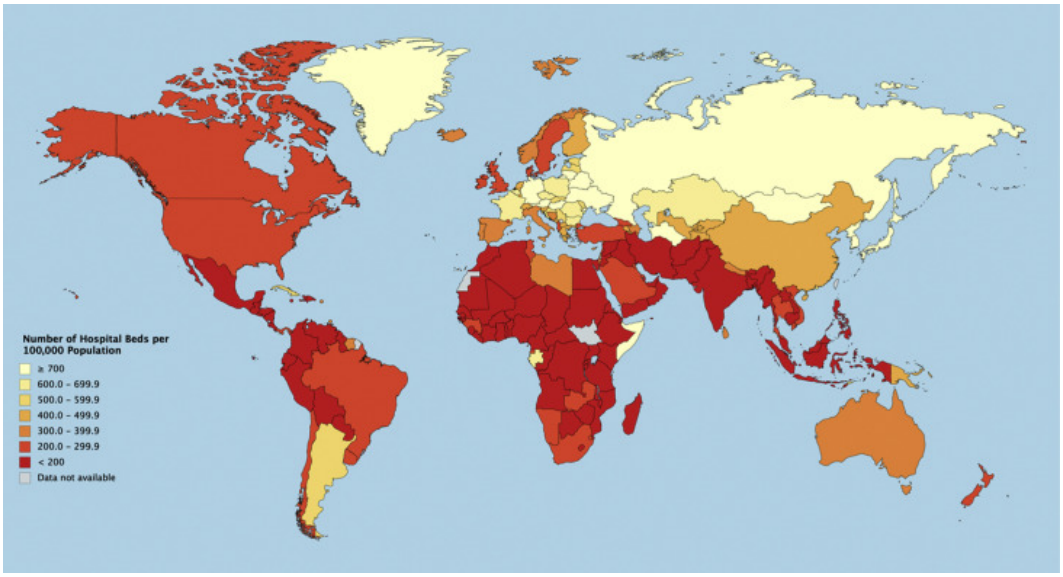
*Cross-checked with midwifery data: Source 'The State of the World's Midwifery (SoWMy) 2021 report' accessed from: https://www.unfpa.org/publications/sowmy-2021

Precise data on global numbers of Obstetricians/Gynaecologists is difficult to obtain. A best-case calculation: if the percent of medical doctors who are Obstetricians/Gynaecologists are extrapolated from North America (5% of medical doctors) and the European Union (4.5% of medical doctors) globally, then in broad strokes, the ratio of Obstetricians/Gynaecologists to 10,000 female patients is: Africa 0.23, Americas 2.3, South-East Asia 0.71, Europe, 3.4, Eastern Mediterranean 1, and the Western Pacific of 1.9.

A significant amount of the work indicated on the previous pages related to care definition, has been performed under resource restrained settings: The numbers of maternal health focused specialists indicated in the tables above do not only focus on PE (see SoWMy report for their focuses) while the other healthcare specialists have to focus on the additional spectrum of needs. In locations where the innovation is planned to be used it needs to be designed to work in it with the available infrastructure already at that location.

Hospital bed capacity

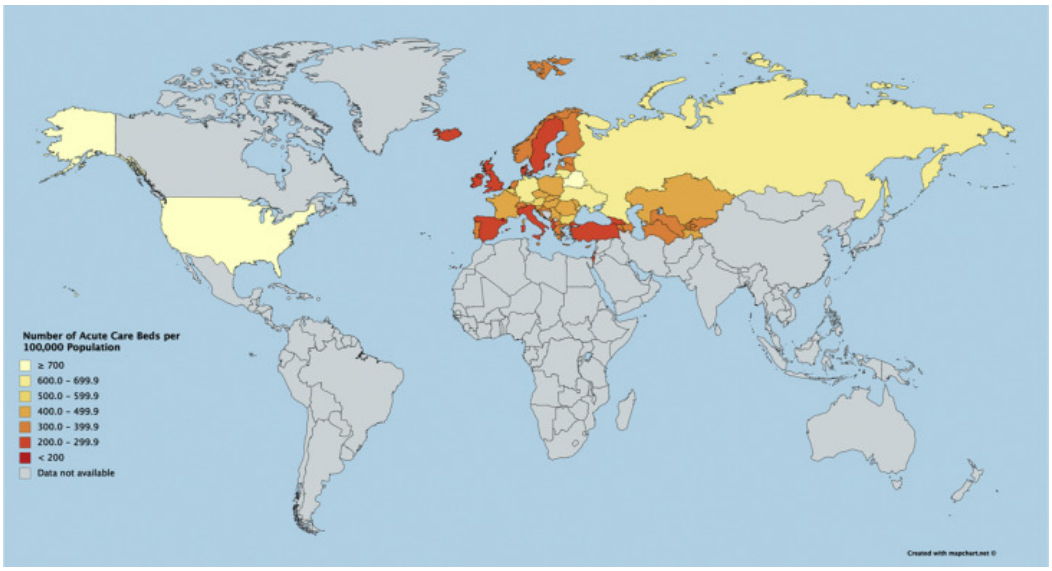
1) Number of hospital beds per 100,000 population



'There are over 10,000 community clinics that could be delivering optimal primary care but more than three-quarters of physician positions currently lie vacant.'

Hossain MM, et al. Revitalising general practice in Bangladesh: complementing 'the Bangladesh Paradox'. Br J Gen Pract. 2018;68(675):482. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145986/

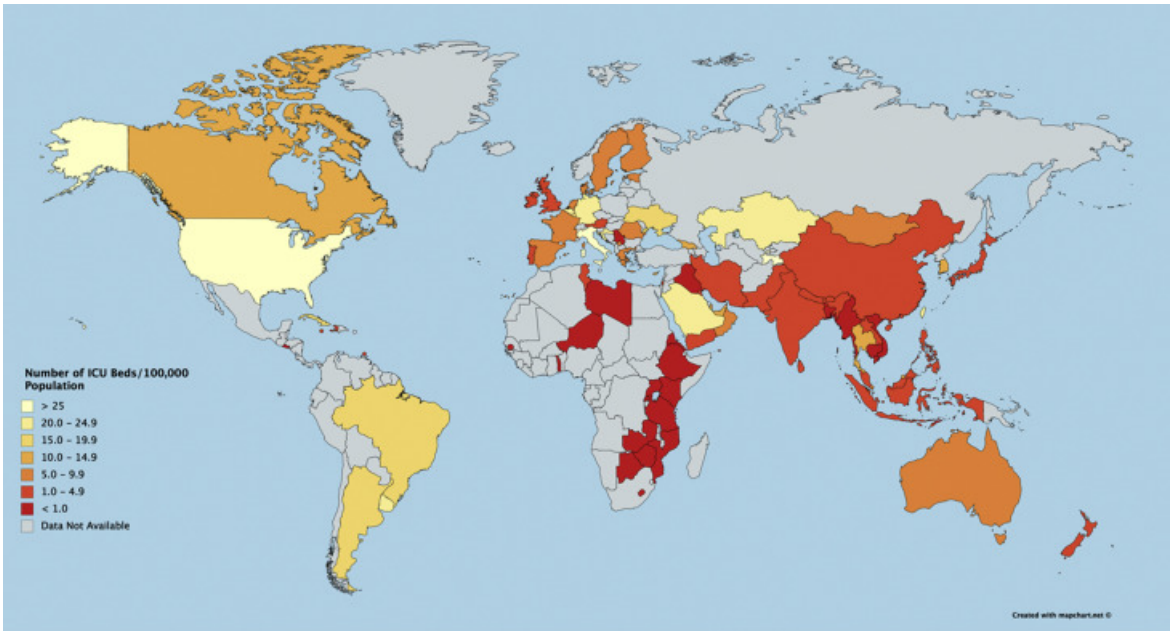
2) Number of acute care beds per 100,000 population



3) Number of ICU beds per 100,000 population

'Severe preeclampsia, eclampsia, and HELLP syndrome are common causes of Intensive Care Unit (ICU) admission among obstetric patients. Because these conditions are life threatening and have high maternal and infant mortality rates, ICU care is recommended when two or more organ systems are failing and there is need for ventilator support.'

Lam MTC, Dierking E. Intensive Care Unit issues in eclampsia and HELLP syndrome. Int J Crit Illn Inj Sci. 2017;7(3):136-141.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613404/



Source of charts: Sen-Crowe B, et al. A Closer Look Into Global Hospital Beds Capacity and Resource Shortages During the COVID-19 Pandemic. J Surg Res. 2021;260:56-63. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685049/ (Reproduced following the copyright and license information published on Elsevier connect)

Section 8: PE initiation and progression and the Patient Journey

Pathophysiology (what is happening)

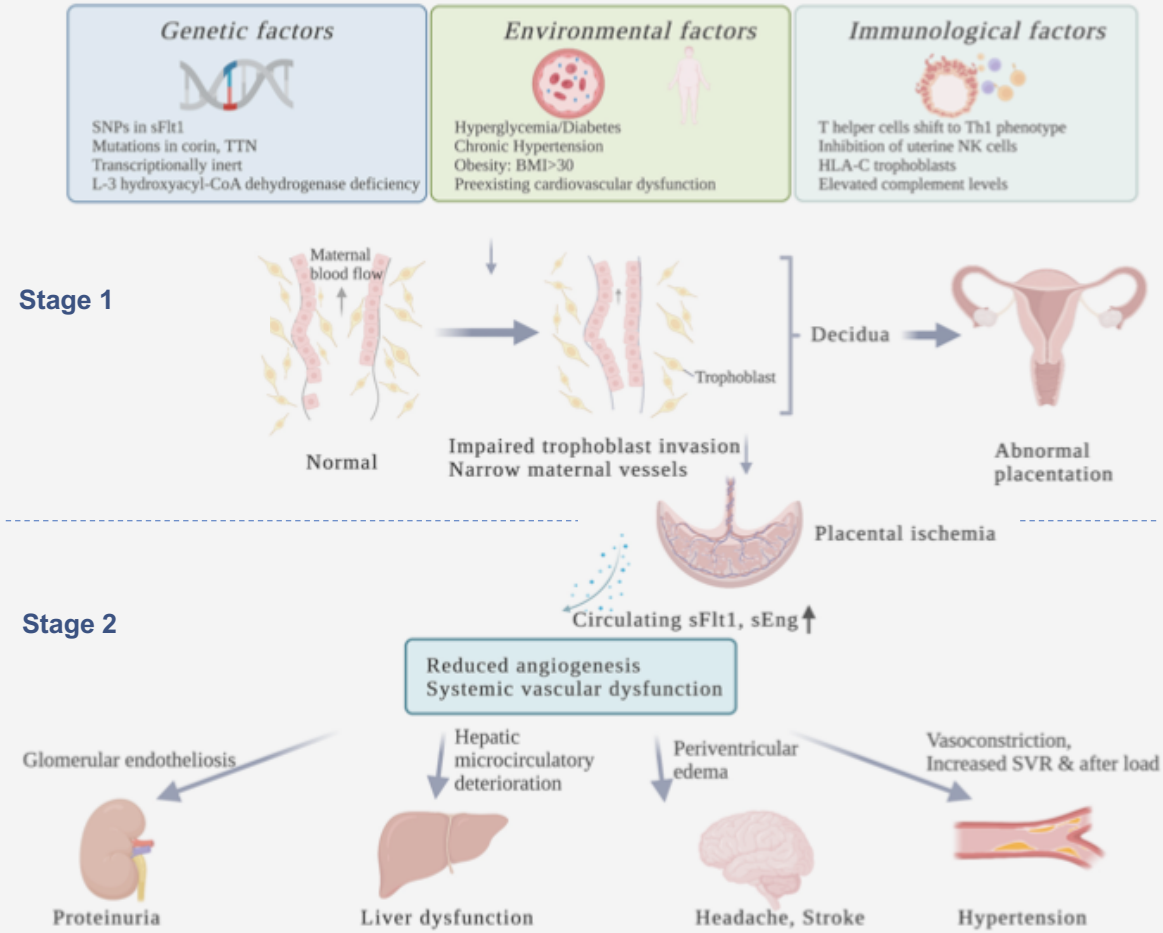


Figure adapted from Qi, J., Wu, B., Chen, X. *et al.* Diagnostic biomolecules and combination therapy for pre-eclampsia. *Reprod Biol Endocrinol* 20, 136 (2022). **Link:** https://rbej.biomedcentral.com/articles/10.1186/s12958-022-01003-3 following the Creative Commons license http://creativecommons.org/licenses/by/4.0/.

Stage 1: The first 12 weeks: Abnormal placentation.

- Inside the walls of the Uterus, are 'Spiral' arteries (named this because they have a spiral structure).
- When an egg implants into the side of the uterus after fertilisation, instead of having their normal temporary role during a menstrual cycle when fertilisation does not occur, the Spiral arteries now have a permanent role for the remaining duration of the pregnancy.
- During the first 12 weeks (the first trimester) of pregnancy, another cell type (trophoblasts) substitutes the existing muscle and endothelial cells that form part of the Spiral artery.
- Muscle and endothelial cells are present in everyone's arteries and normally constrict or dilate the blood vessel while maintaining vessel integrity as a function of need.
- The Trophoblast substitution (named 'Trophoblast Invasion') changes the action of the arteries to reduce the maternal blood flow resistance, and enable an easier transfer of nutrients into the embryo and then foetus prior to neonate delivery.
- In patients with the characteristic risk factors indicated on page 3, this substitution does not always occur, meaning that the maternal arteries do not change, which can result in restricted blood flow and nutrients delivery.
- This creates growth restrictions for the embryo (intrauterine restrictions, due to decreased nutrients), and a stress on the maternal endothelial cells. This creates systemic inflammation with mediators originating from the placenta.

Stage 2: Weeks 13–36/Delivery: Maternal syndrome.

- Because of the systemic inflammation, during this time (the second and third trimesters) a decreased blood flow occurs to the maternal organs.
- Every organ in your body (Female and Male) needs a steady flow of nutrients through regulated blood flow; the decreased blood flow in PE results in multi organ damage or failure and a high risk of death for the mother.

Pathogenesis (when does it happen)

Similar to the great majority of diseases, rare or not, disease pathogenesis is only starting to be understood, because it varies significantly from person to person, occurring in mild or severe forms.

PE in patients can occur, overall, in a combination of 4 pathogenic possibilities:

<34 weeks: early onset	>34 weeks: late onset
Moderate risk	Moderate risk
High risk: 20%, Severe cases	High-risk

*(*there is another division at late stages of pregnancy named term or preterm, of 37 weeks+ or 34–36 weeks)*

If the risk is moderate, healthcare errs towards monitoring to try to wait for a natural or assisted childbirth at normal term (term = expected time of delivery).

If the risk is high, healthcare needs are increased, during the whole pregnancy **into the postpartum period**: if the circumstance becomes too severe preterm, an emergency surgery is planned to remove the placenta, giving rise to premature delivery, with both or either of the mother and the neonate ending in intensive care.

Early onset with high-risk typically results in severe disease occurring with an average frequency of 20% of PE cases.

Similarly moderate risk patients may develop PE or not present with PE at all during the pregnancy period.

All 4 patient groups needing monitoring:

- Early onset and high-risk manifests with severe symptoms typically presenting at around 20 weeks (But biologically starting earlier),
- Moderate risk patients can transition to high risk, and need to be monitored (develop late-onset PE)

If it is a high-risk pregnancy the number of visits and specialist involvement can be significantly greater than the recommended 8 antenatal visits.

The patient needs to be monitored, because the development of PE can be fatal or create significant long-term health issues.

Overviews of PE

Magee LA et al, Preeclampsia, N Engl J Med 2022;386:1817-32. **Link**: https://www.nejm.org/doi/pdf/10.1056/NEJMra2109523

Ives CW, et al. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 ;76(14):1690-1702.**Link:** https://pubmed.ncbi.nlm.nih.gov/33004135/

Erez O, et al. Preeclampsia and eclampsia: the conceptual evolution of a syndrome. Am J Obstet Gynecol. 2022;226(2S):S786-S803. **Link:** https://pubmed.ncbi.nlm.nih.gov/35177220/

Rana S, et al. Preeclampsia: Pathophysiology, Challenges, and Perspectives. Circ Res. 2019;124(7):1094-1112. Link: https://pubmed.ncbi.nlm.nih.gov/30920918/

Wu P, et al. Preeclampsia and Future Cardiovascular Health: A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes. 2017;10(2):e003497. **Link:** https://pubmed.ncbi.nlm.nih.gov/28228456/

Korzeniewski SJ, et al The Global Pregnancy Collaboration (CoLab) symposium on short- and long-term outcomes in offspring whose mothers had preeclampsia: A scoping review of clinical evidence. Front Med (Lausanne). 2022;9:984291. **Link**: https://pubmed.ncbi.nlm.nih.gov/36111112/

Fingar KR et al. Delivery Hospitalizations Involving Preeclampsia and Eclampsia, 2005–2014: statistical brief No. 222. H-CUP, Agency for Healthcare research and Quality. April 2017. Accessed from: https://www.hcup-us.ahrq.gov/reports/statbriefs/sb222-Preeclampsia-Eclampsia-Delivery-Trends.pdf

Patient journey experience

The personal journey of a patient with PE is very different to the clinical pathway: they obviously intersect but the emphasis is totally different. A detailed study was performed from 2016 to 2020 in patients with PE (the full description of the study and outcomes can be found in the links below, including a graphical representation on the preeclampsia.org website). There are several outcomes and characteristics of the study that should inform innovators on unmet needs:

- Prenatal education on risk factors, signs and symptoms
- Awareness of PE and patient communication/involvement
- Postpartum risk and warning sign education
- Maternal mental health and wellbeing and awareness of PPD
- Long-term health impacts
- Support on family planning

The study was performed by questionnaire, created with an educational level understanding for people of 9–13 years of age (indicated as eighth grade level in the article): this has ramifications for every innovation.

Bijl RC, et al. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. BMJ Open. 2022;12(3):e057795. **Link**: https://pubmed.ncbi.nlm.nih.gov/35241475/

The preeclampsia patient journey. The Preeclampsia Foundation, last updated May 10 2022, accessed November 2022: https://preeclampsia.org/patientjourney

Section 9: Clinical Care

For an innovator wanting to start their design process and see if their idea could have an impact in clinical care, an excellent resource on PE has been produced by the California Maternal Quality Care Collaborative (CMQCC).

Druzin M et al, Improving Health Care Response to Hypertensive Disorders in Pregnancy, a California Maternal Quality Care Collaborative Improvement toolkit, 2021. Link: https://www.cmqcc.org/resources-tool-kits/toolkits/HDP

It is phenomenally comprehensive, including training simulations, executive level quality improvement suggestions. For an innovator thinking of clinically focused solutions, the PE focused care pathway algorithms located in the appendices are great starting points to understand the care pathways, actions and resources used. You can define your idea to see what kind of innovation you will generate and if your solution will add benefit to the patients' outcome, the HCPs job, the healthcare process. The toolkit is based on a very highly resourced infrastructure, that can enable an innovator identify those that can be adapted for more resource constrained locations.

Direct-resource/infrastructure needs:

1.Antenatal visits: Family doctor, community care centre (or equivalent)

Tests: Urinalysis (Proteinuria test), blood pressure measurement, uterine artery ultrasound (Doppler), PAPP-A, PlGF test, creatinine test

Physical location requirements: private office, clinical/diagnostic lab set-up, examination room (local clinic, mobile clinic, community care centre or equivalent)

Expertise: Family doctor, community care specialist, nurse, sonographer for ultrasound if used and no other specialist available

Medicines: aspirin, magnesium sulphate (if severe PE suspected), calcium supplement, antihypertensives (Hydralazine, Nifedipine, Labetalol, Methyldopa)

Note: if PE is diagnosed, care is recommended to be transferred to obstetricians immediately

2.Hospital care (acute or urgent care, delivery)

Tests: Urinalysis (Proteinuria test), blood pressure measurement, uterine artery ultrasound (Doppler), PAPP-A, PlGF test, potential liver tests and coagulation studies, urine tests, creatinine test

Physical location requirements: birthing suite, surgical suite (normally in same location as birthing suite), neonatal unit, neonatal intensive care unit

Expertise: Nurse, midwife, obstetrician, sonographer for ultrasound if used and no other specialist available, surgical team if c-section performed, neonatal intensive care team

Medicines: aspirin, magnesium sulphate, calcium supplement, antihypertensives (Hydralazine, Nifedipine, Labetalol, Methyldopa)

3.Postpartum: community care centre (or equivalent) if non-severe postpartum

Tests: blood pressure measurement

Physical location requirements: private office, clinical/diagnostic lab set-up, examination room (local clinic, mobile clinic, community care centre or equivalent)

Expertise: Obstetrician, Paeditrician, Family doctor, community care specialist, nurse

Medicines: antihypertensives (Hydralazine, Nifedipine, Labetalol, Methyldopa), ACE inhibitor postpartum if on methyldopa previously, magnesium sulphate

Important - the lists above are:

- Non-exhaustive
- Do not account for country specific experts or locations
- Do not account for resource availability
    - Resource availability: this is indicated as a barrier to healthcare in virtually every guide or report read on hypertension and PE. Applies to physical, staff and solutions in all geographies.
    - Treatments: In LMIC access to and availability of quality validated medicines is a barrier: many primary care locations indicate shortage of Magnesium sulphate
    - Diagnostic solutions: shortage of dipsticks for proteinuria assessment or clinically validated, field tested and regulatory approved ultrasound imaging devices are not widely available in primary care locations in LMIC (see: von Dadelszen, P et al 2021, below in LMIC references)

In the LMIC specific references below, staff, location and resources used for healthcare in PE have typically been reported by the authors.

Post-partum depression (PPD) has a higher prevalence in patients with PE.

Global post-partum mental health *after normal delivery* has been assessed through systematic reviews, with prevalence ranging from 3–38% prevalence, across 40 countries from every continent. *The prevalence in China in this report was 14%.*

See figure 3 of:

Hahn-Holbrook J, et al. Economic and Health Predictors of National Postpartum Depression Prevalence: A Systematic Review, Meta-analysis, and Meta-Regression of 291 Studies from 56 Countries. Front Psychiatry. 2018 Feb 1;8:248. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5799244/

In a study of Chinese patients with PE from 2021, normal pregnancy mothers reported similar PPD prevalence. Patients with PE were reported to have significantly higher levels of PPD (at least double the prevalence of PPD in normal pregnancy) as a function of severity of the PE, preterm birth, whether fetal growth restriction had been observed and if the neonate had to be moved to NICU.

See Table 7 of:

Ye Y, et al. Preeclampsia and Its Complications Exacerbate Development of Postpartum Depression: A Retrospective Cohort Study. Biomed Res Int. 2021;2021:6641510. **Link:** https://pubmed.ncbi.nlm.nih.gov/33977108/

The combined insights of the 2 articles above would suggest PPD impacts every geography for patients with PE.

The needs of patients with PPD

Caropreso L, et al. Preeclampsia as a risk factor for postpartum depression and psychosis: a systematic review and meta-analysis. Arch Womens Ment Health. 2020 Aug;23(4):493-505. **Link:** https://pubmed.ncbi.nlm.nih.gov/31802249/

Mbarak, B., et al. Postpartum depression among women with pre-eclampsia and eclampsia in Tanzania; a call for integrative intervention. BMC Pregnancy Childbirth 19, 270 (2019). **Link:** https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-019-2395-3

McNab, S.E., et al. The silent burden: a landscape analysis of common perinatal mental disorders in low- and middle-income countries. BMC Pregnancy Childbirth 22, 342 (2022). **Link:** https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-022-04589-z#citeas

Umamah F, et al. The effectiveness of psycho-educational counseling in pregnant women with preeclampsia: A systematic review. J Public Health Res. 2022;11(3):22799036221104161. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9335477/

LMIC reported experiences in implementing PE focused care

Meazaw MW, et al. Health Care Readiness in Management of Preeclampsia/Eclampsia in Ethiopia: Evidence from National Facility-Based Survey. Risk Manag Healthc Policy. 2022;15:1225-1241. **Link**: https://pubmed.ncbi.nlm.nih.gov/35734013/

Mekie M, et al. (2022) Perception towards preeclampsia and perceived barriers to early health-seeking among pregnant women in selected Hospitals of South Gondar Zone, Northwest Ethiopia: A qualitative study. PLoS ONE 17(8): e0271502. **Link**: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0271502

Dempsey A, et al. Pathways to service access for pre-eclampsia and eclampsia in rural Bangladesh: Exploring women's care-seeking. PLoS One. 2021;16(2):e0245371. **Link**: https://pubmed.ncbi.nlm.nih.gov/33539410/

Williams A, et al. Management of Preeclampsia, Severe Preeclampsia, and Eclampsia at Primary Care Facilities in Bangladesh. Glob Health Sci Pract. 2019 6;7(3):457-468. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6816814/

Gomathy E., et al. Early onset and late onset preeclampsia-maternal and perinatal outcomes in a rural teritiary health center. Int J Reprod Contracept Obstet Gynecol. 2018;7(6):2266-2269. **Link:**https://www.ijrcog.org/index.php/ijrcog/article/view/4744

von Dadelszen P, et al. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. Lancet. 2020;396(10250):553-563. **Link** https://pubmed.ncbi.nlm.nih.gov/32828187/

Ernawati K et al, Contributing Factors of Neonatal Death from Mother with Preeclampsia in Indonesia. Indian Journal of Public Health Research & Development, October 2018, Vol. 9, No. 10, 405–409. **Link:** https://repository.unair.ac.id/105758/1/8.%20Contributing%20Factors%20of%20neonatal%20Death%20from%20Mother%20with%20Preeclampsia%20in%20Indonesia.pdf

Yushida Y, Zahara E. The Risk Factors toward Preeclampsia Events of Pregnant Women in Meureubo and Johan Pahlawan Community Health Center West Aceh. Open Access Maced J Med Sci [Internet]. 2020 [cited 2022 Oct. 25];8(E):670-3. Available from: https://oamjms.eu/index.php/mjms/article/view/5531

Lazo-Vega L et al , ACOG and local diagnostic criteria for hypertensive disorders of pregnancy (HDP) in La Paz-El Alto, Bolivia: A retrospective case-control study,The Lancet Regional Health - Americas, Volume 9, 2022, 100194, **Link:** https://www.sciencedirect.com/science/article/pii/S2667193X22000114

Salam RA, et al. Diagnosis and management of preeclampsia in community settings in low and middle-income countries. J Family Med Prim Care. 2015;4(4):501-6.link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4776599/

von Dadelszen, P et al. Management of Preeclampsia in Low- and Middle-Income Countries: Lessons to Date, and Questions Arising, from the PRE-EMPT and Related Initiatives. Maternal-Fetal Medicine: 2021 - Volume 3 - Issue 2 - p 136-150. **Link**: https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

Warren, C.E., et al. A primary health care model for managing pre-eclampsia and eclampsia in low- and middle- income countries. Reprod Health 17, 46 (2020). **Link**: https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-020-0897-0

Section 10: Awareness and Education: The Bottleneck

'The Patient Journey Survey was created to be at eighth grade reading level (13–14 years of age).'

Bijl RC, et al. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. ***Link****: https://pubmed.ncbi.nlm.nih.gov/35241475/*

This quote is essential: most humans do not understand the complex biology of disease or ramifications of effective healthcare: this is not surprising; most people stop studying biology in their early teenage. Throughout the great majority of PE or maternal health articles referenced in this briefing, even in the most high-tech focused articles, there is a common thread: ***lack of awareness***. The innovation will not be used if they don't know what it is for, and how it will help. This requires tailoring communicated information so that they understand it.

In some LMIC countries from both a clinical care and awareness the following barriers have been reported and are going to have an added impact on innovative solutions designed to target this bottleneck (all information obtained from LMIC references above):

- Age of getting pregnant, also based on difference in cultural definition of age of being an adult.
- Time of first visit to medical specialist, for many locations is >20 weeks of pregnancy
- Beliefs, family and local cultural influence, often driven by male leaders, and/or male determined opinions, driven, unwillingly into the functional behaviour of elder females.

Awareness operates at 3 levels: the Patient, the HCP, the Partner, and channel usage needs to be tailored for each one

The Patient

Patient awareness and education is essential but difficult: most humans only think about their health when they start to feel ill, not because there is a risk that they may become ill.

Ideally with PE you want the patient to be aware before they become pregnant, especially if there are risks. As the 'Patient Journey' research referenced above indicated:

- 75% preeclampsia patients were aware of the term, but not the symptoms
- Recommended that all pregnant patients should be educated about the signs and symptoms of PE and know what to report.
- Whether they fall into the risk group

The design of educational focused innovation in communication for maternal healthcare may be facilitated by 2 studies on the educational preferences of hypertensive disorders of pregnancy.

Roth, H., et al. Exploring education preferences of Australian women regarding long-term health after hypertensive disorders of pregnancy: a qualitative perspective. BMC Women's Health 21, 384 (2021).
Link: https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-021-01524-w

Gholami K et al. Impact of Educational Interventions on Knowledge About Hypertensive Disorders of Pregnancy Among Pregnant Women: A Systematic Review. Frontiers in Cardiovascular Medicine. 2022; 9. 886679.
Link: https://www.frontiersin.org/articles/10.3389/fcvm.2022.886679/full

Points considered with weightings in these articles include:

- Use of graphics
- Patient focused education programmes
- Level of detail
- How relatable is the content?
- Is it consistent across sources?
- Is it easy to understand?
- Is it in multiple languages?
- How visible is it, is it easy to find?
- Channels of communication (this applies across all groups in this section)
- Education on self-monitoring, including using approved at-home point-of-care solutions
- Does it address cultural or sensory (hearing or vision) related factors?
- How most patients want to hear it initially communicated to them by an HCP

Resources do exist for HCPs to communicate information to patients: For example, all of the Patient Association websites, and also MSD manuals (amongst others) that has multilingual (11 different languages) patient focused version information on:

- High blood pressure during pregnancy, in long and quick fact formats: https://www.msdmanuals.com/home/women-s-health-issues/pregnancy-complicated-by-disease/high-blood-pressure-during-pregnancy
- PE, in long and quick fact formats: https://www.msdmanuals.com/home/women-s-health-issues/complications-of-pregnancy/preeclampsia-and-eclampsia

Do the HCPs know reliable resources exist? Do the partners of the patient? Does the community?

Using QR codes

QR codes, scanned through mobile device cameras are much easier than hyperlinks or web addresses that need to be copied and pasted, while flyers need resources and time to distribute, often with them being rapidly discarded.

Scanning a QR code through a device will automatically direct the viewer to the information you want. You can also make it a voyage of discovery: one code leads to a short message, with QR codes leading to 'know more about this subject'.

QR codes can be put everywhere: at locations, specifically targeting locations or things people see (next to the self-test pregnancy products of pharmacies, side of beer can, on a petrol pump, condom packets, as a flyer at fast food locations in LMIC countries, on the side of box used for trainers package of a menstruation product, … the options are discrete, limitless and strategic: a QR code in a health congress can direct HCPs towards education sites, one in a community care centre can direct parents, partners and family towards awareness tools)

The HCP

There are a broad array of globally available guides and resources, that evidence suggests are not being used.

If the preference of the patient is to hear it from the HCP first, but they may not know of its existence, this means that the HCP cannot make the patient aware.

All the guidelines and resources read for this briefing are of exceptional quality, and written by KOLs and Patient Associations, as both internationally reviewed standards and as direct step-by-step instructions on what to do in all health care settings.

What could be the reasons why is awareness or usage so low?

1) Time availability: The 'healthcare infrastructure availability' section above has a direct impact: and the innovator should not be misled by the numbers, healthcare in wealthier countries is also understaffed. A solution designed for LMIC may well have broader impacts, whereas the inverse maybe limiting.

   a) International variations in primary care physician consultation time

      'One hundred and seventy-nine studies were identified from 111 publications covering 28 570 712 consultations in 67 countries. Average consultation length differed across the world, ranging from 48 s in Bangladesh to 22.5 min in Sweden. We found that 18 countries representing about 50% of the global population spend 5 min or less with their primary care physicians.'

      Irving G, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open* 2017;7:e017902. **Link**: https://bmjopen.bmj.com/content/7/10/e017902

      A blood pressure test takes at least 1 minute

   b) Decisions on patients' health is urgent.

      The existing guides as they stand are copy heavy: a specialist needs the time to read them. They may have this time available; in the context of a consultation, they need something short, an algorithm to hand for whichever innovation or process they are using. A patient with PE is not the only patient they will see, so they need to be able to quickly switch from one to another, with no decrease in care quality.

2) Language: If a mentally exhausted HCP has only 43 seconds, then educational resources need to be in local languages and dialects, while also addressing cultural sensitivities. Facilitating increased awareness for the HCP, enables them to explain it to the patient, who will almost definitely only speak the national language or local dialect fluently.

   Public administration staff are not multilingual, their IT systems unreliable, and the understaffing of healthcare everywhere means 'hoping' one of them has the time to translate the latest guide is a stretch. Solutions exist for translation. *This is the responsibility of the innovator*: When designing your innovation, make multi-lingual an integral part of it.

   See '*The Preeclampsia Foundation*' website: they use a solution that enables information to be communicated in 135 different languages and dialects: it is possible.

3) Understanding: Teachers also need to be taught.

   If the average consultation time in Bangladesh is 43s, this means in a working day a family doctor will possibly see over 300 different patients:

   Solutions for capacity building & continued professional development in primary care have been reported

   Warren, C.E., et al. A primary health care model for managing pre-eclampsia and eclampsia in low- and middle- income countries. Reprod Health 17, 46 (2020). **Link**: https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-020-0897-0

   While page 24 of the FIGO first trimester guidelines clearly illustrates why this approach needs to extend into tertiary care

   Poon LC et at. A Pragmatic Guide for First-Trimester Screening and Prevention: Compiled FIGO. Int. J. Gynaecol Obstet. 2019; 145 Suppl 1. Link: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.12802

Some of this requires a capital investment, that many locations do not have. As highlighted in the opening quote to 'IT infrastructure' below: innovative solutions to tele-education, as well as tele-medicine, may create significant benefit.

From **a mobile based education solution** perspective, one resource does seem to stand out: the online MSD Manuals that has a catalogue of resources an HCP could use to talk to a patient. As all content is written by specialists in the field, it is written voluntarily, routinely reviewed, and no branded solution is permitted to be advertised, one has to anticipate impartiality. It also has an Obstetrics professional version 'app' version (in English), that can be downloaded onto mobile devices.

See: https://www.msdmanuals.com/professional/resourcespages/mobileapps

The Partner

The patient is pregnant and has the risk to become severely ill, the HCPs are overwhelmed: the partners (and families/communities) need to become more involved, even with the other responsibilities they may have. They are the only other people available. Because the other option is if their partner dies or has long-term morbidity because of PE, their short-term perspectives are going to make life a lot more complicated.

Educating the partner on their role is therefore essential…it has also been proven to be possible

Insights from the studies below on partner involvement in antenatal care and PE, are illuminating, because despite the barriers, it is possible and has huge benefit.

All studies should be read if the innovator is focusing on this (there are also a large amount of published evidence not referenced here that can be read: search term 'male involvement maternal healthcare).

The study of Mapunda et al analysed a) cultural norms and gender roles, b) ignorance of reproductive health service, c) factors outside their control, d) couple interaction and conflicts, and e) institutional obstacles. Revealing that men's (partners) involvement in antenatal care can be high if:

- They have access to antenatal care education
- There are standards of structure and process of antenatal service
- Their role is well defined in the maternal health care system.

The study of Lusambili AM, et al. details facilitators and barriers (self-perception, community perception of them and socioeconomic barriers): the study of Zakaria et al while reported specifically for two rural counties in Kenya, reveal that these observations apply equally across cultures and urban settings. But the study also revealed that discussions with HCPs increased partner support and care.

There seems to be a common vein that stretches across cultures and economic status, that an innovator can explore to enable healthcare benefit.

Tele-education designed for HCPs (see below) could also be repurposed as tele-education for partners: if education is done in groups, within one centre, but in web conferences with many other centres, may be some of the cultural barriers described in the publications below for partner engagement may be resolvable.

Culturally sensitive and tailored information, in channels and resources designed that will inform them on:

- Is your partner at risk?
- What signs of symptoms you need to look out for?
- How care has changed since your parent's time?
- The importance of the first trimester antenatal check up
- What actions you can do to reduce stress and PE incidence for your partner?
- What you should do if your partner manifests symptoms?
- Digital communication solutions that help and enable your partner
- *Differentiating local remedies from modern healthcare (culture/location specific)*
- *Homogenising and enhancing vocabulary to better understand the symptoms (culture/location specific)*
- *The positive actions the community can take (culture/location specific)*

Machenje AS et al. Knowledge and Myths about Preeclampsia and Eclampsia and its Influence on Antenatal Service Utilization among Pregnant Women and their Male Partners in Mtwara Regional - Tanzania: A Cross Sectional Analytical Study. Archives of Internal Medicine Research 5 (2022): 397–411. **Link** https://www.fortunejournals.com/articles/knowledge-and-myths-about-preeclampsia-and-eclampsia-and-its-influence-on-antenatal-service-utilization-among-pregnant-women-and-t.html

Mapunda B, et al (2022) Prevalence and barriers to male involvement in antenatal care in Dar es Salaam, Tanzania: A facility-based mixed-methods study. PLoS ONE 17(8): e0273316. **Link:** https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0273316

Dempsey A, et al. Pathways to service access for pre-eclampsia and eclampsia in rural Bangladesh: Exploring women's care-seeking. PLoS One. 2021;16(2):e0245371. **Link:** https://pubmed.ncbi.nlm.nih.gov/33539410/

Tessema KM, et al (2021) The association between male involvement in institutional delivery and women's use of institutional delivery in Debre Tabor town, North West Ethiopia: Community based survey. PLoS ONE 16(4): e0249917. **Link:** https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0249917

Lusambili AM, et al. Male Involvement in Reproductive and Maternal and New Child Health: An Evaluative Qualitative Study on Facilitators and Barriers From Rural Kenya. Front Public Health. 2021;9:644293. **Link** https://pubmed.ncbi.nlm.nih.gov/33968883/

Zakaria M, et al. Women's Perception of Male Involvement in Antenatal, Childbirth and Postnatal Care in Urban Slum Areas in Bangladesh: A Community-Based Cross-Sectional Study. Healthcare (Basel). 2021 Apr 16;9(4):473. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8073583/

Section 11: Diagnostics & Screening

Development of precisely a new diagnostic, especially if it is based on molecular signals for a rare disease needs to be carefully considered. The overriding point is that the final product used to measure the molecular signal must:

- Integrate into the existing care pathway and make diagnosis more accurate
- Be easy to use within the actual infrastructure, with little or no specialisation required
- It must also have sufficient patient specific statistical evidence to prove sensitivity and specificity.

Statistics/Biostatistics measurements:

You need to to identify the solutions diagnostic yield: basically, does the diagnostic provide the info needed.

1) Sensitivity and specificity: you must be able to differentiate patients. This is typically done comparing the existing gold standard with your innovation (high false signals stop development)

	Subjects with the disease	Subjects without the disease
Positive	True positive	False positive
Negative	False negative	True negative

2) Predictive values: measuring probability of having the disease in a defined population.

3) Accuracy measurements: this data is essential and ideally should be stratified for the relevant populations: -

- Likelihood ratios
- Receiver Operating Characteristic
- Diagnostic odds ratio vs. Youden's index: two different methods that compare two or more diagnostic tests

Data management and security is also a critical consideration, especially in low resource settings:

> Numerous diagnostic products have been sent back to drawing board by regulatory authorities following due diligence of data management processes and methods that have not adhered to all the standards used for quality control and patient data privacy (these are different standards to those for medicines).

For PE, diagnostic product innovation is impacted by two geographic issues: validation in markets where new innovations can be purchased and application in markets where high-cost diagnostics cannot be purchased and potentially implemented due to infrastructure.

PE is also impacted by screening vs diagnostic factors in known at-risk patients. Not all patients at-risk will develop PE but no-one wants to diagnose too late because of the avoidable very serious adverse effects on the patient.

If the at-risk patient is identified sooner, hospitalisation, monitoring and lifestyle changes can reduce risk of development of severe forms.

Meaning, once a patient has been identified as at-risk using a new solution or market, they need to be monitored more closely using existing or newly developed follow up procedures.

Despite the obvious need for proven clinical benefits, it also needs to be demonstrated to be cost-effective. Precisely:

1. A hospital runs processes based on standards-of-care that confer benefits considered to be the best they can offer with the funds they have
2. A new innovation demonstrates it can provide a better quality of care
3. This means the care procedure has to change: does this require changes to training, resources, time spent in healthcare facilities throughout the whole care pathway from initial diagnosis to post-partum care?
4. If this does result in a better-quality care and reduced prices, when are these felt?
5. Are locations using the same processes uniformly, and can alternatives render new solutions obsolete

Case study:

In PE, the example of PlGF measurements, First Trimester Screening and Aspirin treatment illustrates this conundrum for innovation design:

At the first antenatal visit combining Maternal characteristics (incl. risk factors) with blood pressure measurements, plus a specific maternal ultrasound measurement with serum measurements of two molecular markers (PAPP-A, and PlGF) can predict PE manifestation in the patient: 89% of most early onset and normally most severe PE (<34 weeks), 75% of moderate or preterm PE (34–37 weeks) and 47% of mild or term (>37 weeks) PE patients.

Those patients with the pertinent measurements therefore need closer monitoring. During follow up in the at-risk patients, including those with late-onset if the ratio of two markers PLGF vs. sFlt-1 are measured it can predict if a patient needs hospitalisation, especially at preterm. This reduces hospitalisation need and essentially neonate intensive care. It has also been used in high-risk early onset patients' diagnosis, but cost-effectiveness is still debated.

If a patient is defined as high-risk early onset high risk of severe disease, daily low dose Aspirin, can reduce the risk of developing PE: Contrary to advice, in some locations, it has been reported, that instead of using highly precise diagnostic processes, they prescribe Aspirin every day, and follow the standard antenatal follow-up, as its easier: they have a right to do this. For an innovator, focusing in diagnostics can creates at unforeseen disruption and a higher risk. Changes in practice therefore always need to be monitored by the innovator.

Diagnostic, screening or monitoring solutions in PE

The following references should aid innovators interested in developing individual solutions

MacDonald TM, et al. Clinical tools and biomarkers to predict preeclampsia. EBioMedicine. 2022;75:103780. **Link:** https://pubmed.ncbi.nlm.nih.gov/34954654/

Dathan-Stumpf A, et al. sFlt-1/PlGF ratio for prediction of preeclampsia in clinical routine: A pragmatic real-world analysis of healthcare resource utilisation. PLoS One. 2022;17(2):e0263443. **Link:** https://pubmed.ncbi.nlm.nih.gov/35202416/

Ohkuchi, A., et al. Economic evaluation of the sFlt-1/PlGF ratio for the short-term prediction of preeclampsia in a Japanese cohort of the PROGNOSIS Asia study. Hypertens Res 44, 822–829 (2021). **Link:** https://www.nature.com/articles/s41440-021-00624-2

Nikuei, P., et al. Diagnostic accuracy of sFlt1/PlGF ratio as a marker for preeclampsia. BMC Pregnancy Childbirth 20, 80 (2020). **Link**: https://pubmed.ncbi.nlm.nih.gov/32033594/

Leaños-Miranda A, et al. Usefulness of the sFlt-1/PlGF (Soluble fms-Like Tyrosine Kinase-1/Placental Growth Factor) Ratio in Diagnosis or Misdiagnosis in Women With Clinical Diagnosis of Preeclampsia. Hypertension. 2020;76(3):892-900. **Link:** https://pubmed.ncbi.nlm.nih.gov/32713272/

Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. Am J Obstet Gynecol. 2022 Feb;226(2S):S1071-S1097.e2. doi: 10.1016/j.ajog.2020.07.020. Epub 2020. **Link**: https://pubmed.ncbi.nlm.nih.gov/32682859/

von Dadelszen P, et al. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. Lancet. 2020;396(10250):553-563. **Link:** https://pubmed.ncbi.nlm.nih.gov/32828187/

OB-GYNs step up preeclampsia prevention by recommending low-dose aspirin for all patients. UTHealth Houston News. Updated February 13 2020, Accessed Nov 2022: https://www.uth.edu/news/story.htm?id=083b33f9-9b1a-4028-9b9f-138556ce99d3

Zeisler H, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016;374(1):13-22. **Link:** https://pubmed.ncbi.nlm.nih.gov/26735990/

Van Doorn R, et al. Dose of aspirin to prevent preterm preeclampsia in women with moderate or high-risk factors: A systematic review and meta-analysis. PLoS One. 2021;16(3):e0247782. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7943022/

Integrated diagnostic, point-of-care and digital health characteristics

The following references are highly recommended if innovators are considering this approach

Evidence assessments

PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio)
NICE Diagnostics guidance [DG49] Published: 27 July 2022. Accessed Nov 2022. https://www.nice.org.uk/guidance/dg49

Approaches developed by local HCPs

Walle M, et al. The Diagnostic Value of Hepatic and Renal Biochemical Tests for the Detection of Preeclampsia Among Pregnant Women Attending the Antenatal Care Clinic at the University of Gondar Comprehensive Specialized Hospital, Gondar, Northwest Ethiopia. Int J Gen Med. 2022;15:7761-7771. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9562986/

Price considerations

McLaren ZM, et al. Cost effectiveness of medical devices to diagnose pre-eclampsia in low-resource settings. Dev Eng. 2017;2:99-106. **Link:** https://pubmed.ncbi.nlm.nih.gov/29276756/

Where they could be rolled out/road-tested

Warren, C.E., et al. A primary health care model for managing pre-eclampsia and eclampsia in low- and middle- income countries. Reprod Health 17, 46 (2020). **Link**: https://reproductive-health-journal.biomedcentral.com/articles/10.1186/s12978-020-0897-0

Insights from what actually worked, and unmet need

von Dadelszen, Peter et al. Management of Preeclampsia in Low- and Middle-Income Countries: Lessons to Date, and Questions Arising, from the PRE-EMPT and Related Initiatives. Maternal-Fetal Medicine: 2021 - Volume 3 - Issue 2 - p 136-150. **Link**: https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

Section 12: Point of care (PoC) diagnostic solutions

A natural approach to reduce costs, increase usability, geographic penetration and increase quality of care provision is the use of point-of-care. For the innovator in PE, interested in PoC, this has added benefit, as publications indicate which key characteristics of the product and the infrastructure in which it was used drove or prevented benefit creation.

From a health technology perspective, key criteria to assess vs. existing solutions typically include:

- Need
- Outcome
- Feasibility
- Type of benefit
- Economic benefit
- Can it be used in the existing infrastructure for the relevant patients within healthcare policy

Key observations of PoC drivers, and while based on LMIC assessments, are probably applicable everywhere were:

- How much training is needed to use it
- Are the outputs easy to interpret
- Is it difficult or costly to maintain
- What is the source and availability of energy
- Is technical support needed
- Sensitivity/Specificity
- Are extra resources needed (private location)

References are based upon evidence reviews or actual study reports of usage, divided according to the main current approaches used in the antenatal process. The publication of ***Mueller et al***, provides a clear insight into PoC validation approaches and evidence collection in resource constrained settings,

Urinalysis

McLaren ZM, et al. Cost effectiveness of medical devices to diagnose pre-eclampsia in low-resource settings. Dev Eng. 2017;2:99-106. **Link:** https://pubmed.ncbi.nlm.nih.gov/29276756/

Lei R, et al. Current and emerging trends in point-of-care urinalysis tests. Expert Rev Mol Diagn. 2020;20(1):69-84. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7365142/

Döbert M, et al. Screening for late preeclampsia at 35-37 weeks by the urinary Congo-red dot paper test. J Matern Fetal Neonatal Med. 2021:1-5. Link: https://pubmed.ncbi.nlm.nih.gov/34182860/

Khaliq, et al. The effectiveness of the Congo red dot paper test in hypertensive disorders of pregnancy in women of African ancestry: A systematic review protocol. Medicine: Case Reports and Study Protocols: 2022 - Volume 3 - Issue 6 - p e0227. **Link:** https://journals.lww.com/md-cases/Fulltext/2022/06000/The_effectiveness_of_the_Congo_red_dot_paper_test.1.aspx

Petca, A., et al. New approaches in predicting and diagnosing preeclampsia: Congo Red Dot Paper Test (Review). Experimental and Therapeutic Medicine, 2022; 23, 270. Link: https://www.spandidos-publications.com/10.3892/etm.2022.11196

Rood KM et al. Congo Red Dot Paper Test for Antenatal Triage and Rapid Identification of Preeclampsia. eClinicalMedicine, 2019; 8, 47-56. **Link:** https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(19)30025-2/fulltext

Ultrasound (doppler)

Mueller, D., et al. Portable continuous wave Doppler ultrasound for primary healthcare in South Africa: can the EUnetHTA Core Model guide evaluation before technology adoption?. Cost Eff Resour Alloc 19, 8 (2021). Link: https://resource-allocation.biomedcentral.com/articles/10.1186/s12962-021-00261-z#Sec23

Agrawal G, et al. A comparative evaluation of portable Doppler ultrasound versus electrocardiogram in heart-rate accuracy and acquisition time immediately after delivery: a multicenter observational study. J Matern Fetal Neonatal Med. 2021;34(13):2053-2060. Link: https://pubmed.ncbi.nlm.nih.gov/31409165/

Blood pressure measurement

von Dadelszen, Peter et al. Management of Preeclampsia in Low- and Middle-Income Countries: Lessons to Date, and Questions Arising, from the PRE-EMPT and Related Initiatives. Maternal-Fetal Medicine: 2021 - Volume 3 - Issue 2 - p 136-150. **Link**: https://journals.lww.com/mfm/fulltext/2021/04000/management_of_preeclampsia_in_low__and.8.aspx

Giblin, L., et al. Effect of the CRADLE vital signs alert device intervention on referrals for obstetric haemorrhage in low-middle income countries: a secondary analysis of a stepped- wedge cluster-randomised control trial. BMC Pregnancy Childbirth 21, 317 (2021). Link: https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/s12884-021-03796-4

Vousden N, et al. Incidence of eclampsia and related complications across 10 low- and middle-resource geographical regions: Secondary analysis of a cluster randomised controlled trial. PLoS Med. 2019;16(3):e1002775. **Link:** https://pubmed.ncbi.nlm.nih.gov/30925157/

Munyungula J, Shakwane S. Self-monitoring of blood pressure for preeclampsia patients: Knowledge and attitudes. Curationis. 2021;44(1):e1-e8. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8517804/

PlGF measurements

McCarthy FP, Gill C, Seed PT, Bramham K, Chappell LC, Shennan AH. Comparison of three commercially available placental growth factor-based tests in women with suspected preterm pre-eclampsia: the COMPARE study. Ultrasound Obstet Gynecol. 2019;53(1):62-67. **Link:** https://pubmed.ncbi.nlm.nih.gov/29575304/

Gullai, N., Stenczer, B., Molvarec, A. *et al.* Evaluation of a rapid and simple placental growth factor test in hypertensive disorders of pregnancy. Hypertens Res 36, 457–462 (2013). **Link**: https://www.nature.com/articles/hr2012206

PlGF-based testing to help diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio)
NICE Diagnostics guidance [DG49] Published: 27 July 2022. Accessed Nov 2022. https://www.nice.org.uk/guidance/dg49

Section 13: Global IT connectivity and availability

Tele-education can be used extensively for medical education in most SSA countries... it can address the challenges associated with the lack of telemedicine expertise among clinicians, ethical and privacy concerns, which were identified as barriers to the successful implementation of telemedicine systems…it can address the challenges associated with the lack of telemedicine expertise among clinicians, ethical and privacy concerns, which were identified as barriers to the successful implementation of telemedicine systems.

Dodoo JE, et al.

Digital health solutions in all their formats are dependent on two infrastructures: fixed connection or fibre optic, that for example would be used for good quality telemedicine, and mobile internet, used for remote monitoring, self-management applications and potential point-of-care IT integrated solutions.

In LMIC, the speed of IT development has meant mobile coverage is being developed faster than fibre optics. For the digitally focused innovator 2 connection availability resources are recommended.

Global mobile internet coverage:

The GSMA mobile connectivity index represents an annual update and map country by country of critical parameters related to connectivity:

- Infrastructure
- Affordability
- Consumer readiness
- Content and services

Link: https://www.mobileconnectivityindex.com/#year=2021

Global internet (fixed and mobile) coverage:

For fixed line and fibre optic availability, the International Telecommunication Union, generates an annual Global Connectivity report, that can be downloaded. It is a thorough and comprehensive assessment in key regions of

- Fixed vs. mobile subscriptions and affordability
- Percent of population using the internet
- Differences between urban and rural areas
- Percent of population within reach of an operational fibre-optic network, by distance

Link: https://www.itu.int/hub/publication/d-ind-global-01-2022/

Evidence of digital healthcare provision in LMIC and a global guide: what works

Known barriers related cost of the subscription, digital literacy across all users and **cost of the device**. But there is space for social innovation and philanthropic entrepreneurship, if there is a motivation.

The possibility to trade-in a device when buying a new one (phone, tablet or computer) could have *an additional option for the customer*: the entity could offer to refurbish, tailor with the needed apps/software and *give it for free to HCPs in LMIC* to distribute to their patients *as a healthcare facilitator* during their diagnosis and treatment period to enable a step towards better care…*an enabling tool.*

The following articles have been selected as they are peer-reviewed and based on evidence obtained through actual usage or systematic reviews of programmes related to *implementation, scaling and sustaining digital health initiatives* in LMICs. While focused on low resource settings, these insights have equal pertinence in wealthier countries, where healthcare resources are also strained (albeit at a different level).

Dodoo JE, et al. The development of telemedicine programs in Sub-Saharan Africa: Progress and associated challenges. Health Technol (Berl). 2022;12(1):33-46. **Link**: https://pubmed.ncbi.nlm.nih.gov/34849325/

Owolabi, E.O., et al. Telemedicine in Surgical Care in Low- and Middle-Income Countries: A Scoping Review. World J Surg 46, 1855–1869 (2022). **Link:** https://link.springer.com/article/10.1007/s00268-022-06549-2

Acharibasam JW, Wynn R. Telemental Health in Low- and Middle-Income Countries: A Systematic Review. Int J Telemed Appl. 2018;2018:9602821. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6241375/

Chitungo I, et al. Utility of telemedicine in sub-Saharan Africa during the COVID-19 pandemic. A rapid review. Hum Behav Emerg Technol. 2021;3(5):843-853. **Link:** https://pubmed.ncbi.nlm.nih.gov/34901772/

Labrique, A.B., et al. Best practices in scaling digital health in low and middle income countries. Global Health 14, 103 (2018). **Link:** https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-018-0424-z

Telehealth around the world: A global guide, from DLA PIPER, written in 2020. *Visit the link, on the right-hand side is 'download pdf' that then permits downloading the full handbook* **Link:** https://www.dlapiperintelligence.com/telehealth/countries/index.html?t=01-availability-of-telehealth

*The implication is that digitally focused solutions, need to be designed to work in a '**Collapsing Venn Diagramme**' of transport routes, patient density, available hotspots of mobile internet coverage, and health care community locations that if do not exist, may need to be constructed, through which patients are filtered between risk and monitoring management, to care centre bed for 24/7 monitoring that will need fibre optic (that can also be used for tele-education and telemedicine centres) to hospitals where acute and intensive care are needed. This is a very different IT set up than that used for most people's daily use: suggesting that for higher innovative impact, solutions for digital health should initially be designed for LMIC, and when proven functional transitioned to wealthier countries.*

PE focused and Maternal Digital health

The references refer to solutions developed and tested to date: whether geographic expansion, updating or further field testing will open avenues for enhanced healthcare could represent the next steps, but in addition to the evidence indicated in previous sections, innovators also need to consider availability and connectivity:

-Digital literacy of the patient
-How easy is it to initiate using the approach
-What is its source, & availability of energy
-Are there evidence requirements needed before roll out
-Can it be used with the existing connectivity
-Motivation of the HCP to want to learn
-Digital literacy of the HCP
-Is technical support needed when it stops working
-Impact of culture or religion on female technology usage
-Family pressure
-Level of training needed
-What happens when a disease impact is indicated

The 3 studies below from the same groups of authors, represent the best case-study and user guide for understanding complete **'design to roll out to validation'** for an on-site digital solution for PE, and probably any indication in LMIC.

von Dadelszen P, et al. The Community-Level Interventions for Pre-eclampsia (CLIP) cluster randomised trials in Mozambique, Pakistan, and India: an individual participant-level meta-analysis. Lancet. 2020;396(10250):553-563. **Link** https://pubmed.ncbi.nlm.nih.gov/32828187/

Boene H, et al. Implementation of the PIERS on the Move mHealth Application From the Perspective of Community Health Workers and Nurses in Rural Mozambique. Front Glob Womens Health. 2021;2:659582. **Link:** https://pubmed.ncbi.nlm.nih.gov/34816216/

Bone JN, et al. Economic and cost-effectiveness analysis of the Community-Level Interventions for Pre-eclampsia (CLIP) trials in India, Pakistan and Mozambique. BMJ Glob Health. 2021;6(5):e004123. **Link:** https://pubmed.ncbi.nlm.nih.gov/34031134/

PE focused

Shahil Feroz A, et al. Exploring digital health interventions for pregnant women at high risk for pre-eclampsia and eclampsia in low-income and-middle-income countries: a scoping review BMJ Open 2022;12:e056130. **Link:** https://bmjopen.bmj.com/content/12/2/e056130

Ngwenya, M. W. , et al. Utilisation of Digital Health in Early Detection and Treatment of Pre-Eclampsia in Primary Health Care Facilities South Africa: Literature Review. In (Ed.), Primary Health Care. IntechOpen.2022. **Link:** https://www.intechopen.com/chapters/80349

Li S, et al. Improving preeclampsia risk prediction by modeling pregnancy trajectories from routinely collected electronic medical record data. NPJ Digit Med. 2022;5(1):68. **Link**: https://pubmed.ncbi.nlm.nih.gov/35668134/

Sanghavi M, et al. Telemedicine may increase visit completion rates in postpartum patients with preeclampsia. PLoS One. 2022;17(10):e0275741. **Link**: https://pubmed.ncbi.nlm.nih.gov/36269782/

Huber K et al. Implementation of a Home Health–Telemedicine Program to Monitor Pregnant Women with Preeclampsia. 2019; 48 (3) Suppl S22. **Link:** https://www.jognn.org/article/S0884-2175(19)30083-8/fulltext#relatedArticles

Kern-Goldberger A, Hirshberg A. Reducing Disparities Using Telehealth Approaches for Postdelivery Preeclampsia Care. Clin Obstet Gynecol. 2021;64(2):375-383. **Link**: https://pubmed.ncbi.nlm.nih.gov/33904843/

van den Heuvel JFM, et al. SAFE@HOME: Cost analysis of a new care pathway including a digital health platform for women at increased risk of preeclampsia. Pregnancy Hypertens. 2021;24:118-123. **Link:** https://pubmed.ncbi.nlm.nih.gov/33813364/

Feroz AS, et al Understanding the Needs of a Mobile Phone–Based Telemonitoring Program for Pregnant Women at High Risk for Pre-Eclampsia: Interpretive Qualitative Description Study
JMIR Form Res 2022;6(2):e32428. Link: https://formative.jmir.org/2022/2/e32428/PDF

Telehealth/mHealth in maternal care

Krishnamurti T, et al. Development and Testing of the MyHealthyPregnancy App: A Behavioral Decision Research-Based Tool for Assessing and Communicating Pregnancy Risk. JMIR Mhealth Uhealth. 2017;5(4):e42. **Link:** https://pubmed.ncbi.nlm.nih.gov/28396302/

Rahman MO, et al. Effects of mHealth Interventions on Improving Antenatal Care Visits and Skilled Delivery Care in Low- and Middle-Income Countries: Systematic Review and Meta-analysis. J Med Internet Res. 2022;24(4):e34061.**Link:** https://pubmed.ncbi.nlm.nih.gov/35451987/

Escobar MF, et al. Experience of a telehealth and education program with maternal and perinatal outcomes in a low-resource region in Colombia. BMC Pregnancy Childbirth. 2022;22(1):604. **Link**: https://pubmed.ncbi.nlm.nih.gov/35906534/

Fazal N, Webb A, Bangoura J*, et al* Telehealth: improving maternity services by modern technology BMJ Open Quality 2020;9:e000895. **Link:** https://bmjopenquality.bmj.com/content/9/4/e000895

NICU

The Hand to Hold patient support group, also has generated an mHealth solution to support parents with children in NICU: https://handtohold.org/resources/hand-to-holds-mobile-app-online-nicu-community/

Digital Literacy: Digital literacy cannot be solved with a user guide. It represents a balanced equation, the components of which become more complex with continued use and expansion. A well-designed digital solution that addresses all needs and creates benefit will generate impact: it will also create a dependency. In healthcare implementation, such as a patient with PE transitioning to a disease state that needs urgent care, if dependency has been created through utility, but then the system fails this will be fatal. Healthcare infrastructures rarely have the resources to dedicate to urgent informatic correction. The question then becomes in additional to ease of use, how easy is it for the users to resolve issues and maintain functionality, without support when a different part of the digital infrastructure fails.

Section 14: New treatments and drug delivery

'The pipeline for new PPH medicines is concerningly limited, lacking diversity, and showing little evidence of novel technologies. Without significant investment in early-phase research, it is unlikely that new products will emerge.'

McDougall et al, Int. J. Gynecol. Obstet. 2022; 158 (Suppl. 1): 31–39

While focusing on postpartum hemorrhage, the conclusion can also be applied to the PE pipeline.

The authors of the above article are members of The Accelerating Innovation for Mothers project (Concept Foundation with Bill & Melinda Gates Foundation, with Policy Cures Research and Burnett Institute) have generated the Maternal Health Medicines Pipeline online database, that is searchable for maternal health solutions in development across 5 significant pregnancy-related conditions.

Link: https://www.policycuresresearch.org/maternal-health-pipeline/

They have also generated detailed report from July 2021 explaining in detail the characteristics and targets of drugs in development, that can be found here:

https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2021/10/04000316/AIM-pipeline-report.pdf

With a detailed analysis, published as part of Special issue of The International Journal of Gynecology and Obstetrics on Improving access to essential medicines to reduce postpartum hemorrhage morbidity and mortality.

McDougall et al. Innovations in the prevention and treatment of postpartum hemorrhage: Analysis of a novel medicines development pipeline database. Int. J. Gynecol. Obstet. 2022; 158 (Suppl. 1): 31–39. **Link:** https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.14200

Approaches divide into

- Chemical entities (most repurposing approach)
- Biologics (equally divided between repurposing and new development
- Dietary supplements (almost exclusively repurposed solutions)

To stimulate conceptualisation of new interventions the following peer reviewed articles are also suggested for the innovator with an associated rationale why they are worth reading?

Awaludin A, et al. Antihypertensive Medications for Severe Hypertension in Pregnancy: A Systematic Review and Meta-Analysis. Healthcare (Basel). 2022;10(2):325. **Link**: https://pubmed.ncbi.nlm.nih.gov/35206939/

Why? Introduces the concept of the PICO framework: Patient, Intervention, Comparator, Outcome

Woo Kinshella ML, Sarr C, Sandhu A, Bone JN, Vidler M, Moore SE, Elango R, Cormick G, Belizan JM, Hofmeyr GJ, Magee LA, von Dadelszen P; PRECISE Network. Calcium for pre-eclampsia prevention: A systematic review and network meta-analysis to guide personalised antenatal care. BJOG. 2022 ;129(11):1833-1843. Link: https://pubmed.ncbi.nlm.nih.gov/35596262/

Why? Systematic reviews provide large scale standardised statistical reviews of existing interventions are very good sources for intervention reflection as they tend to cut through the hype/best presented data and focus on evidence and the best controlled and structured trials: in this case a focus on calcium

Liabsuetrakul T, Yamamoto Y, Kongkamol C, Ota E, Mori R, Noma H. Medications for preventing hypertensive disorders in high-risk pregnant women: a systematic review and network meta-analysis. Syst Rev. 2022;11(1):135. Link: https://pubmed.ncbi.nlm.nih.gov/35778751/

Why? Same rationale as above, this time focused on hypertension.

Pepe GJ, Albrecht ED. Novel Technologies for Target Delivery of Therapeutics to the Placenta during Pregnancy: A Review. Genes (Basel). 2021;12(8):1255. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8392549/

Why? Slightly more cutting edge, addressing which methodologies are being considered for drug delivery. Intervention validation through clinical study will at some point involve a pregnant woman. Targeting therapies, not just molecularly but also physically may address key ethical concerns of *de novo* development.

Section 15: Costs of PE care

Costs in the US:

These have been widely reported. Combined maternal and neonate healthcare costs are reported to increase, from:
23,035 USD at 37 weeks or longer (gestational age at delivery)
to
311,701 USD at <28 weeks of gestational age at delivery

Neonate related costs representing a significant value the earlier the delivery (Stevens et al, link below) with observations confirmed by at least two other studies.

Stevens et al. Short-term costs of preeclampsia to the United States health care system. Am J Obstet Gynecol. 2017; 217 (237-48.e1-16). **Link:** https://www.ajog.org/article/S0002-9378(17)30561-6/fulltext

Hao J, et al. Maternal and Infant Health Care Costs Related to Preeclampsia. Obstet Gynecol. 2019 Dec;134(6):1227-1233. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6882523/

Li R, et al. Medical expenditures for hypertensive disorders during pregnancy that resulted in a live birth among privately insured women. Pregnancy Hypertens. 2021;23:155-162. **Link**: https://pubmed.ncbi.nlm.nih.gov/33418425/

Costs in the EU:

Only one detailed study exists, across 3 EU countries and the UK, that enters into more details of cost breakdown: it did not report on equivalent 12-month infant related costs, and only to NICU and neonatal ward costs.

Only high-risk patient costs were reported. Following the same approach as that used by Violago CJG et al in the Philippines (*see next page*), the costs for high-risk PE in the EU and UK were modelled.

Table 5: Modelled costs for PE care in EU and UK settings (all values reported in euros)

	UK	NL	IRL	SE
First visit				
regular antenatal care	1263	662	355	557
cost of new screening	150	150	150	150
subtotal	1413	812	505	707
Monitoring				
personnel	3750	1950	2640	1680
ultrasound	1890	705	165	1515
subtotal	5640	2655	2805	3195
Treatment				
aspirin (full duration)	2	2	2	2
calcium supplement (full duration)	19	19	19	19
subtotal	21	21	21	21
Delivery				
cost of care	2967	2967	2967	2967
subtotal				
Normal delivery	2783	2373	704	2319
needing NICU (daily price)	9228	7692	5460	16182
normal neonatal ward	6792	4320	3060	7320
subtotal	18803	14385	9224	25821
Caesarian delivery	5104	4531	1058	4755
needing NICU (daily price)	9228	7692	5460	16182
normal neonatal ward	6792	4320	3060	7320
subtotal	21124	16543	9578	28257
Est. total cost with normal delivery	28844	20840	15522	32711
Est. total cost with Caesarian	31165	22998	15876	35147
Est. total cost of no PE	11083	10072	8096	9913

To model this (because we wanted to know) we assumed the following for high-risk patients: routine monitoring approach required, and following identification has high-risk, 15 anticipated visits between first screen and delivery at 37 weeks, plus the NICU/neonatal ward requirement used in the article for their cost-effectiveness analysis (duration in NICU). For both normal or caesarian delivery, the neonate would be monitored in NICU prior to movement to standard neonatal care. Costs for no-PE were based on only 8 visits, no treatment, normal delivery, and two days of normal neonatal ward care before discharge. When modelled of delivery at 28 weeks and associated costs (infant costs related to NICU, total costs related to care were not too disparate from those reported by Stevens et al for the US in 2017: data not shown because information of that sensitivity would need to be reviewed prior to publications).

Zakiyah N, et al; IMPROvED Consortium. Early cost-effectiveness analysis of screening for preeclampsia in nulliparous women: A modelling approach in European high-income settings. PLoS One. 2022;17(4):e0267313. **Link** https://pubmed.ncbi.nlm.nih.gov/35446907/

Costs in South-East Asia

The example from a private hospital in South-East Asia (Philippines, Private Tertiary Care centre)

Prices were presented as a function of testing the ACOG First Trimester Screening (FTS): PlGF, PAPP-A, ultrasound measurement of uterine artery pulsatility (UtA-PI) and maternal characteristics assessment, combined with Aspirin treatment.

Table 6: costs of PE care at a private Philippine's hospital

Approach for High-Risk PE* incl. FTS	Price in Philippine Peso	USD Price (Nov. 2002 exchange rate)
Early PE/ Caesarian section delivery	159,680	2712
Late PE/ Caesarian section delivery	143,580	2439
No PE/ Caesarian section delivery	79,993	1359
Early PE/ Spontaneous delivery	129,680	2203
Late PE/ Spontaneous delivery	113,580	1929
No PE/ Spontaneous delivery	49,993	850

**Low risk PE followed the same approach as High-Risk, but were not prescribed Aspirin (price of 588 Philippine Peso lower than indicated, or 10 USD). ACOG First Trimester Screening costed at 9450 Philippine Peso or 160.5 USD. Table adapted from Violago CJG et al, link below.*

The article associated with this table, is uniquely useful, as the authors present with significant detail exactly which resources were used for each patient group.

Violago C J G et al. Cost-effectiveness analysis of first trimester screening for preeclampsia and early initiation of aspirin therapy for prevention of the disease in a private tertiary hospital. Philippine Journal of Obstetrics and Gynecology. 2021.45(2)2: 47-54 **link**: https://www.pogsjournal.org/temp/PhilippJObstetGynecol45247-3405091_092730.pdf

Costs in Latin and South-America

Costs could not be found, but combined with the treatment algorithms indicated earlier in the briefing, and the detail from the Violago CJG et al, and Zakiyah N, et al articles these should be easy to estimate for the innovator. Health cost catalogues can be found online for healthcare in Latin and South-America that will permit the innovator to estimate alternate geography cost burdens and market sizes.

Costs in African countries

No comprehensive healthcare costs could be identified. Costs identified were related to health care procedures for PE, were related to early diagnostics: Blood pressure measurement and proteinuria for diagnosis of PE.

- Proteinuria costs ranged from 0.2 USD per test, with concomitant low sensitivity and specificity, to nearly 13 USD per test at 2015 USD equivalents, with higher sensitivity/specificity.
- Blood pressure tests all had very low costs (all less than 0.30 USD per test) with expected sensitivity/ specificity, but initial outlay costs for the devices are unknown.

McLaren ZM, et al. Cost effectiveness of medical devices to diagnose pre-eclampsia in low-resource settings. Dev Eng. 2017;2:99-106. **Link:** https://pubmed.ncbi.nlm.nih.gov/29276756/

Reported PPD associated costs (non-PE specific).

The cost impacts of PPD have been reported from at least two locations (refs below).

- UK: health/social care costs amounted to 1688 GBP and productivity losses of 2514 GBP to the mother.

  Bauer A et al. The costs of perinatal mental health problems. Centre for Mental Health and London School of Economics. Date: 2014 (accessed Nov 2022). https://www.centreformentalhealth.org.uk/Handlers/Download.ashx?IDMF=07afd94b-92cb-4e47-8439-94cbf43548d8

- US: annual cost of untreated perinatal mood and anxiety disorder of 6400 USD, of which 3253 USD were related to the mother (33% were related to productivity loss, 20% to maternal health expenditures and 5% to Obstetric specific costs). An additional 2080 USD costs were incurred due to child related needs.

  Luca DL et al. Society costs of Untreated Perinatal mood and anxiety disorders in the United States. M50 Mathematica Policy Research. Issue brief. Last updated April 2019. Accessed from: https://mathematica.org/news/new-study-uncovers-the-heavy-financial-toll-of-untreated-maternal-mental-health-conditions

Longer term health costs related to sequelae of organ morbidity or cardiovascular events have not been reported exclusively for patients who have recovered from PE.

Section 16: Some final considerations for the innovator:

Join the dots: before designing, consider the whole ecosystem and the actors in it. Look at solutions that have been designed and rolled out, but maybe not expanded. If innovations are adapted, made multi-lingual combined, and those opportunities definitely exist for PE based on the work that has been done already by all the stakeholders; don't forget it still needs validation in a clinical setting.

PICO: Patient population, Intervention(product), Comparator, Outcome, should be applied to every type of product. The broader the impact the product, the more data and sensitivity you will need, especially if it's anything non-interventional that potentially results in a medical intervention. Rare disease patient populations are heterogeneous: their low number means precise pathogenesis is often incomplete, and as indicated above pathogenesis greatly impacts the type of innovation and its design.

Factor that in: you may consider your innovation to be applicable to a whole Rare Disease patient population, but often solutions are applicable to specific symptoms, age groups, phases or stages and underlying morbidities, or other SDOH related risks that the patient may be exposed to, some of which may be responsible for an idiopathic occurrence.

There is always a comparator, even in Rare Diseases, where interventions do not currently exist. In addition to direct clinical impacts, is your planned product reducing caregiver related burdens and costs, does it reduce burden on HCPs and/or processes, or will it increase the needs for more specialists and dedicated facilities, is your solution equitable, are you addressing the needs of one stakeholder, many or all of them?

Health Economic and Outcomes Research (HEOR): the aspect a lot of Innovators think about too late, it is not the same as clinical outcome, take a short online course on it or HTA to introduce it to yourself. While review and approval bodies are not always national or centralized, the economic evidence assessments they use tend to be based on the same concepts and then adjusted locally. Note that perspectives and calculations of value differ between locations (QALYs vs DALYs, differing PROMs, accepted outcomes).

The ISPOR US Healthcare System Overview-Decision makers and influencers gives a good illustration of what is needed from the pharmacoeconomic angle: https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview

While global country information, where available, can be found at their around the world section https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines

Note that most of these only apply to therapeutic application, med tech, diagnostics, healthcare process, and now digital health, have differing requirements and are often not nationally homogenous.

Social determinants of health and wealthy countries vs. LMIC

Many available existing sources of information do not include every stakeholder or perspective, and some innovators may not know where to look, to complete the picture. Especially when evidence is generated in different geographies with different healthcare infrastructures e.g., Universal healthcare vs private or hybrid, timing and location of evidence generation and influence of Social Determinants of Health (SDOH) on the patient, their journey, quality of life, available care or infrastructure and epidemiological data.

This is relevant for all countries irrespective of overall recognised income status. With this perspective, it may make the identification and development of innovative solutions for Rare Diseases global by design: solutions designed for wealthy countries (even if incidence and prevalence maybe influenced by socioeconomic status, ethnicity and gender within them), where available specialised Rare Disease healthcare is sparse, and SDOH and lifestyle risks can symptoms, may with partnering and redesign be applicable for patients with Rare Diseases in Low- and Middle-Income Countries, where resources are even more stretched, and *vice versa*.

Appendix 1: What's being clinically tested:

In clinical trials at time of writing (November 2022), that might complement the AIM study (also include devices, mental health, imaging, diagnostics)

Search location: clinicaltrials.gov
Condition or disease: Preeclampsia, Pre-eclampsia

Filters:

- **Recruiting** (not yet recruiting, recruiting, enrolling by invitation, active not recruiting)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4

NCT Number	Phases	Status	Interventions	Enrollment
NCT04632589	Early Phase 1	Recruiting	Drug: Losartan Potassium|Drug: Placebo	20
NCT03482440	Early Phase 1	Recruiting	Drug: Salsalate Oral Tablet|Drug: Placebo Oral Tablet	32
NCT04243278	Early Phase 1	Recruiting	Drug: Low-dose aspirin|Drug: Placebo oral tablet	44
NCT04153760	Early Phase 1	Recruiting	Drug: Aspirin 81 mg|Drug: Placebo	384
NCT01717586	Phase 1	Active, not recruiting	Drug: Pravastatin|Drug: Placebo	48
NCT05232994	Phase 1	Not yet recruiting	Drug: Esomeprazole 20mg	38
NCT05119101	Phase 1	Recruiting	Drug: Dexamedotomidine added to Magnesium sulfate|Drug: Magnesium sulfate	100
NCT04979793	Phase 1	Recruiting	Drug: L-citrulline|Drug: Placebo	338
NCT04103489	Phase 1	Recruiting	Drug: Eculizumab	15
NCT04645004	Phase 1|Phase 2	Active, not recruiting	Drug: Aspirin 81Mg Non-enteric coated Tab	20
NCT04303806	Phase 2	Not yet recruiting	Drug: rosuvastatin	80
NCT03667326	Phase 2	Recruiting	Drug: Aspirin|Drug: Placebo oral capsule	90
NCT03978767	Phase 2	Recruiting	Drug: Ibuprofen 600 mg|Drug: Ketorolac|Drug: Acetaminophen|Drug: Oxycodone	286
NCT03893630	Phase 2	Recruiting	Drug: Acetylsalicylic Acid 81 mg|Drug: Acetylsalicylic Acid 162 mg|Other: Control	250
NCT04402385	Phase 2	Recruiting	Drug: Aspirin 81 mg|Drug: Placebo	490

NCT02989025	Phase 2	Recruiting	Drug: 17 OHPC	60
NCT04873596	Phase 2	Recruiting	Drug: Nebulized dexmedetomidine|Drug: Nebulized midazolam	94
NCT03961360	Phase 2|Phase 3	Recruiting	Drug: Aspirin 81 mg|Drug: Aspirin 162 mg	220
NCT03944512	Phase 3	Active, not recruiting	Drug: Pravastatin|Other: Placebo	1550
NCT03350516	Phase 3	Active, not recruiting	Dietary Supplement: Daily 500 mg elemental calcium as calcium carbonate|Dietary Supplement: Daily1500 mg elemental calcium as calcium carbonate	22000
NCT05287321	Phase 3	Not yet recruiting	Drug: Hydroxychloroquine	122
NCT04762992	Phase 3	Not yet recruiting	Drug: subcutaneous Enoxaparin|Other: standard of care	120
NCT04182373	Phase 3	Recruiting	Drug: Antithrombin gamma|Drug: physiological saline	180
NCT04070573	Phase 3	Recruiting	Drug: acetylsalicylic acid	400
NCT04298034	Phase 3	Recruiting	Drug: Labetalol, Nifedipine	300
NCT04551807	Phase 3	Recruiting	Procedure: Modified natural cycle|Procedure: Programmed cycle	788
NCT05253781	Phase 3	Recruiting	Drug: Low-dose aspirin|Other: Placebo	476
NCT03298802	Phase 3	Recruiting	Drug: Hydrochlorothiazide 50mg Tablet|Drug: Placebo Tablet	612
NCT04356326	Phase 3	Recruiting	Drug: Aspirin 150 mg|Drug: Placebo	500
NCT04392375	Phase 4	Active, not recruiting	Drug: Nifedipine 30 MG|Drug: Placebos	110
NCT04343235	Phase 4	Enrolling by invitation	Drug: furosemide|Drug: labetalol	140
NCT04656665	Phase 4	Not yet recruiting	Drug: Aspirin	600
NCT04631627	Phase 4	Not yet recruiting	Drug: Aspirin	1500
NCT05294952	Phase 4	Not yet recruiting	Genetic: real time PCR	82
NCT04424693	Phase 4	Not yet recruiting	Drug: Tdap Vaccine Administration	1600
NCT05460416	Phase 4	Not yet recruiting	Drug: Acetylsalicylic acid	3000
NCT05309460	Phase 4	Not yet recruiting	Drug: Labetalol Oral Tablet|Drug: NIFEdipine ER	600
NCT05139238	Phase 4	Not yet recruiting	Drug: Labetalol|Drug: Nifedipine	280
NCT04479072	Phase 4	Recruiting	Drug: Aspirin 81 mg|Drug: Placebo	180
NCT05221164	Phase 4	Recruiting	Drug: Aspirin 162 mg	200

NCT03735433	Phase 4	Recruiting	Drug: 162mg aspirin dose	200
NCT04908982	Phase 4	Recruiting	Drug: Aspirin 81mg	60
NCT04797949	Phase 4	Recruiting	Drug: Low-dose aspirin	156
NCT03570632	Phase 4	Recruiting	Drug: Metformin	60
NCT04441073	Phase 4	Recruiting	Drug: Lignocaine|Drug: Placebo	100
NCT05049616	Phase 4	Recruiting	Drug: ACE Inhibitors and Diuretics|Drug: NIFEdipine ER	60
NCT02531490	Phase 4	Recruiting	Drug: Labetalol|Drug: Nifedipine|Drug: Methyldopa	368
NCT03824119	Phase 4	Recruiting	Drug: Ibuprofen 600 mg|Other: Standard Postpartum Care without NSAIDs	200
NCT04236258	Phase 4	Recruiting	Drug: NIFEdipine ER|Drug: Enalapril	90
NCT03342014	Not Applicable	Active, not recruiting	Device: Ultrasound|Biological: Blood sample collection	2159
NCT03018132	Not Applicable	Active, not recruiting	Other: mental health screening, education and referral program	200
NCT04273854	Not Applicable	Active, not recruiting	Device: OMRON Evolv¬Æ blood pressure monitor (Blue-tooth¬Æ enabled) & Proprietary Smartphone POP-HT app¬Æ	200
NCT04864249	Not Applicable	Active, not recruiting	Device: SNOO|Other: Safe sleep education in the postpartum period	110
NCT04660032	Not Applicable	Active, not recruiting	Behavioral: Nudge	222
NCT02412696	Not Applicable	Active, not recruiting	Device: Positive Airway Pressure|Other: Nasal Dilator Strips	262
NCT05521776	Not Applicable	Not yet recruiting	Procedure: First-trimester preeclampsia screening (FMF triple test)	14500
NCT05580523	Not Applicable	Not yet recruiting	Drug: Aspirin 75mg|Drug: Metformin 1.5g|Drug: Aspirin 150 mg|Drug: Placebo	3000
NCT05564988	Not Applicable	Not yet recruiting	Other: Preconditionning	58
NCT05228002	Not Applicable	Not yet recruiting	Other: sFlt-1/PlGF ratio	160
NCT04699825	Not Applicable	Not yet recruiting	Other: Cardiovascular and immunological changes	20
NCT05514847	Not Applicable	Not yet recruiting	Drug: Aspirin 81Mg Ec Tab|Drug: Aspirin 162Mg Ec Tab	150
NCT05554185	Not Applicable	Not yet recruiting	Dietary Supplement: aspirin 100mg and probiotics 1 bag	338
NCT04520048	Not Applicable	Not yet recruiting	Procedure: Laser Doppler coupled with acetylcholine iontophoresis|Procedure: Aortic central pressure and the carotid-femoral pulse wave velocity|Other: Vascular biomarker assay	154
NCT04855513	Not Applicable	Not yet recruiting	Drug: Metformin	414
NCT05534932	Not Applicable	Not yet recruiting	Device: Remote Patient Monitoring	70
NCT05035498	Not Applicable	Not yet recruiting	Drug: Phenylephrine|Drug: Norepinephrine	72
NCT05035485	Not Applicable	Not yet recruiting	Drug: Phenylephrine|Drug: Norepinephrine	32

NCT04576663	Not Applicable	Not yet recruiting	Drug: Normal saline|Drug: Phenylephrine	95
NCT05284474	Not Applicable	Not yet recruiting	Diagnostic Test: soluble fms-like tyrosine kinase to placental growth factor ratio (sFlt-1/PlGF)	598
NCT05533996	Not Applicable	Not yet recruiting	Diagnostic Test: ultrasound	206
NCT05124327	Not Applicable	Not yet recruiting	Other: QI project- usage of RPM	30
NCT05035472	Not Applicable	Not yet recruiting	Drug: Phenylephrine|Drug: Norepinephrine	80
NCT05457504	Not Applicable	Not yet recruiting	Behavioral: Remote blood pressure monitoring|Behavioral: Usual Care	200
NCT03585738	Not Applicable	Not yet recruiting	Dietary Supplement: Inositol + Folic acid|Dietary Supplement: Folic acid	80
NCT03941886	Not Applicable	Recruiting	Other: Low-dose aspirin in women with high risk of preeclampsia	68250
NCT04958057	Not Applicable	Recruiting	Behavioral: SAIL	100
NCT02923206	Not Applicable	Recruiting	Device: TheraSorb sFlt-1 adsorber	23
NCT05056701	Not Applicable	Recruiting	Other: annual follow-up during 10 years	400
NCT04412681	Not Applicable	Recruiting	Diagnostic Test: Enhanced PE Screening	1000
NCT04092829	Not Applicable	Recruiting	Procedure: FROZEN EMBRYO TRANSFER IN SUBSTITUTED CYCLE	1200
NCT05056467	Not Applicable	Recruiting	Procedure: Induction of Labor	825
NCT03509272	Not Applicable	Recruiting	Device: remote monitoring	2000
NCT05021692	Not Applicable	Recruiting	Behavioral: Web-based support program for pregnant women with preeclampsia based on the Health Promotion Model	90
NCT03231657	Not Applicable	Recruiting	Diagnostic Test: Placental biomarkers	2536
NCT03749044	Not Applicable	Recruiting	Other: Patient Educational Tool	80
NCT04766866	Not Applicable	Recruiting	Diagnostic Test: sFlt1/PlGF screening in maternal blood at 35 to 36.6 weeks of gestation	9132
NCT04676295	Not Applicable	Recruiting	Behavioral: Face-to-face and web-based lifestyle intervention	400
NCT04755322	Not Applicable	Recruiting	Drug: Hydroxychloroquine|Drug: Folic acid|Drug: Low-dose aspirin|Drug: Placebo	50
NCT04713228	Not Applicable	Recruiting	Device: ARTSENS Pen	50
NCT04556370	Not Applicable	Recruiting	Drug: Normal saline|Drug: Norepinephrine	92
NCT04989075	Not Applicable	Recruiting	Other: Oral prophylactic intervention	880
NCT05434195	Not Applicable	Recruiting	Dietary Supplement: Arcofolin¬Æ 5-Methyltetrahydrofolate|Dietary Supplement: Arcofolin¬Æ Placebo	128
NCT05558969	Not Applicable	Recruiting	Drug: pregnant women taking magnesium|Drug: Placebo	30
NCT04514276	Not Applicable	Recruiting	Other: consecutive fetoneonatal healthcare pathway	828
NCT03487185	Not Applicable	Recruiting	Device: Continuous Positive Airway Pressure|Other: Sleep Advice Control	1500

NCT04604535	Not Applicable	Recruiting	Dietary Supplement: Concentrated beetroot juice|Dietary Supplement: Placebo	320
NCT04291313	Not Applicable	Recruiting	Dietary Supplement: Vitamin D3 (90¬µg)|Dietary Supplement: Vitamin D3 (10¬µg)	2000
NCT03858595	Not Applicable	Recruiting	Device: Self monitoring of blood pressure using Health Gauge Device and monthly monitoring of weight gain	70
NCT05524259	Not Applicable	Recruiting	Dietary Supplement: Myo-inositol and routinely recommended folic acid|Dietary Supplement: Routinely recommended folic acid	464
NCT05241327	Not Applicable	Recruiting	Dietary Supplement: Beetroot Juice	80
NCT04998942	Not Applicable	Recruiting	Behavioral: virtual cardiac wellness program|Behavioral: Placebo comparator	100
NCT04580927	Not Applicable	Recruiting	Behavioral: Breastfeeding self-efficacy (BSE)	323
NCT05159726	Not Applicable	Recruiting	Other: Video Education	150
NCT03309826	Not Applicable	Recruiting	Device: Positive Airway Pressure|Device: Nasal Dilator Strip	80

Appendix 2: Innovation development costs (ball park figures: US Marketplace, unknown for LMIC) and pricing considerations for rare diseases

- Rapid POC diagnostic development: 1.4 million USD
- Standard in vitro diagnostic development: 2.5 to 2.8 million USD
- App or Wearable technology development: 425,000 to 500,000 USD
- Electronic Healthcare Record: 150,000 USD
- Health Tracker: 200,000 USD
- Imaging agent: 100 to 150 million USD
- New software solution for imaging platform: 50,000 to 400,000 USD
- Orphan drug (chemical entity/new molecular entity type) 250 million USD (*see Berdud et al, Jayasundara et al refs below*). This changes as a function of whether:
    - the drug is a biologic (antibody, peptide) or an advance therapy medical product (gene therapy, bioengineering)
    - If the rare disease is oncology focused or not (rare oncological diseases have similar patient number requirements as frequent oncological, whereas on average for orphan drugs 2 to 5 fold lower requirement in patient number based on phase of development)

Many analyses that look at drug development costs, do not address downstream costs, these typically include:

- Multiple clinical trial requirements within and across geographies
- Level of uniqueness of solution (costs can significantly increase to address statistical relevance, long-term impact and evidence requirements if significantly different to existing standard-of-care)
- Post approval studies can cost approximately a further 6 million USD.
- Manufacturing costs
- Distribution and marketing/sales

Similar to all healthcare products, but more consequential for rare diseases it is almost impossible to obtain total market penetration due to healthcare infrastructures and reimbursement approaches, this is a significant barrier to innovation.

In the US for many rare diseases, the patient is seen by a specialist who covers all indications in the same tissue, in Universal healthcare infrastructures, the patient is often referred to a dedicated centre.

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