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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary materials

Appendix 1 – Methods for rapid review

A rapid review of documents related to the inclusion of pregnant and lactating women in clinical trials was conducted, including:

1) The review of ethics and good clinical practice documents was limited to global guidance. Documents were searched for by title in websites of major international organizations: Council for International Organizations of Medical Sciences (CIOMS), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, World Medical Association (WMA), World Health Organization (WHO). The following documents were reviewed: Declaration of Helsinki (WMA 2013), Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks (WMA 2016), Operational Guidelines for Ethics Committees that Review Biomedical Research (WHO 2000), Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation (WHO 2005), Standards and operational guidance for ethics review of health-related research with human participants (WHO 2011), Ethical Issues in Patient Safety Research: Interpreting Existing Guidance (WHO 2013), Guidance for managing ethical issues in infectious disease outbreaks (WHO 2016), Ethical standards for research during public health emergencies: Distilling existing guidance to support COVID-19 R&D (WHO 2020), Responding to the global mpox outbreak Ethics issues and considerations. A policy brief (WHO 2023), Guidance for research ethics committees for rapid review of research during public health emergencies (WHO 2020). For included documents see Table S1.
2) The review of documents from 23 national regulatory authorities included in the WHO Listed Authority (WLA) (https://www.who.int/initiatives/who-listed-authority-reg-authorities) considered at maturity levels 3 and 4 covering both vaccines and medicines, and transitioning country authorities (categories of B (SRA medicines), C (highly performing NRA vaccines) and E (functional NRA vaccines) as of 07 March 2024. The following listed authorities were searched:
    - National Medical Products Administration (NMPA), China
    - Egyptian Drug Authority (EDA), Egypt
    - Food and Drugs Authority, Ghana
    - Central Drugs Standard Control Organisation (CDSCO), India
    - National Agency of Drug and Food Control (BADAN POM), Indonesia
    - National Agency for Food and Druga Administration and Control (NAFDAC), Nigeria
    - Ministry of Food and Drug Safety (MFDS), Republic of Korea
    - Saudi Food and Drug Authority (SFDA), Saudi Arabia
    - Medicines and Medical Device Agency (ALIMS), Serbia
    - Health Sciences Authority (HSA), Singapore

- South African Health Products Regulatory Authority (SAHPRA), South Africa
- Food and Drug Administration (FDA), Thailand
- Turkish Medicines and Medical Devices Agency (TITCK), Turkey
- Tanzania Medicines and Medical Devices Authority (TMDA), United Republic of Tanzania
- Vaccine regulatory system, Vietnam
- Therapeutic Goods Administration (TGA), Australia
- Federal Agency for Medicines and Health Products (FAMPH), Belgium
- Health Canada, Canada
- Agence nationale de sécurité du médicament et des produits de santé (ANSM), France
- Agenzia italiana del farmaco (AIFA), Italy
- Medicines Evaluation Board (MEB), Netherlands
- The Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
- Food and Drugs Authority, USA

For identified studies see Table S2.

3) A targeted search of publicly available reports and meeting procedures from international, regional and national expert groups and organizations included the following websites: Academy of Medical Sciences, Berman Institute of Bioethics, Birmingham Health Partners Centre for Regulatory Science and Innovation, Concept Foundation, European Medicines Agency, Global Forum on Bioethics in Research, National Academies of Sciences, Engineering, and Medicine, and National Institute of Child Health and Human Development, and World Health Organization. For relevant documents see Table S3.

Table S1: List of key global ethics and good clinical practice guidance with specifications on pregnancy and lactation

Title of document (year of publication)	Inclusion of women of child-bearing potential	Women who become pregnant during research	Pregnancy	Lactation
Ethics				
International Ethical Guidelines for Health-related Involving Humans. Guidelines 18 and 19 (2016).[31]	√	√	√	√
Good Clinical Practice				
ICH-S5 (R3) Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals (last updated May 2023).[32]	√	√	√	√
Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (2016).[33]			√	√
ICH Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2) (2009).[34]			√	
Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation (2005).[35]		√		

Table S2: List of key guidance documents focused on pregnancy and lactation from regional and national regulatory authorities*

Setting	Authority	Title of document (year of publication)	Focus of the document		
			Pre-clinical studies	**Labelling of medicinal product**	**Post-authorisation surveillance**
Europe	European Medicines Agency (EMA)	Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation (2008).[42]		√	
		Guideline on the Exposure to Medicinal products during pregnancy (2005).[43]			√
	Heads of Medicines Agencies (HMA)	Guideline on Good Vigilance Practices for pregnant and breastfeeding women (2019 – for public consultation).[44]			√
		Guideline on good pharmacovigilance practices (GVP). Module XVI Addendum III – Pregnancy prevention programme and other pregnancy-specific risk minimisation measures (2021).[45]	√		
United States of America	U.S. Food and Drug Administration (FDA)	Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Guidance for Industry (2018).[46]			
		Clinical Lactation Studies: Considerations for Study Design. Draft Guidance for Industry (2019).[47]	√		
		Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format. Draft Guidance for Industry (2020).[48]		√	
		Postapproval Pregnancy Safety Studies. Draft Guidance for Industry (2019).[49]			√

* Listed in WHO Listed Authority (WLA) as maturity levels 3 and 4, and transitioning countries (categories of B (SRA medicines), C (highly performing NRA vaccines) and E (functional NRA vaccines)), as of 07 March 2024.

Table S3. List of relevant reports and meeting procedures from international, regional and national expert groups and organizations

Academy of Medical Sciences[58] Understanding pregnancy: Accelerating the development of new therapies for pregnancy-specific conditions; 2024. https://acmedsci.ac.uk/file-download/5618046
Birmingham Health Partners Centre for Regulatory Science and Innovation[17] Healthy Mum, Healthy Baby, Healthy Future. The Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy; 2022. https://www.birminghamhealthpartners.co.uk/wp-content/uploads/2022/05/Final-Healthy-Mum-Healthy-Baby-Healthy-Future-Report-AW_Accessible-PDF-REDUCED-FILE-SIZE.pdf
Concept Foundation[26] Accelerating innovations for mothers. Medicines for pregnancy specific conditions. Research, development and market analysis. 2021 https://www.conceptfoundation.org/concept-foundation/medicines-for-pregnancy-specific-conditions/
European Medicines Agency[20] Workshop on benefit-risk of medicines used during pregnancy and breastfeeding; 2020. https://www.ema.europa.eu/en/news/workshop-safe-use-medicines-during-pregnancy-and-breastfeeding
Global Forum on Bioethics in Research[18] Meeting Report: Ethics of Research in Pregnancy. Buenos Aires, Argentina, 3-4 Nov. 2016 https://gfbr.global/wp-content/uploads/2017/04/GFBR-2016-report-ethics-of-research-in-pregnancy-FINAL.pdf
National Academies of Sciences, Engineering, and Medicine[39,51,52] *Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks*. Washington, DC: The National Academies Press. 2024. https://doi.org/10.17226/27595. Research with pregnant and lactating persons: Mitigating risk and liability: Proceedings of a workshop—in brief. Washington, DC: The National Academies Press. 2023. https://doi.org/10.17226/27595 Inclusion of Pregnant and Lactating Persons in Clinical Trials: Proceedings of a Workshop. Washington, DC: The National Academies Press.2022. https://doi.org/10.17226/26790
Task Force on Research Specific to Pregnant Women and Lactating Women[66] Taskforce on Research Specific to Pregnant Women and Lactating Women- Report to Secretary, Health and Human Services. 2018. NIHR. https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf

List of Figures

[Figure 1 title: Major obstacles to clinical trials during pregnancy and lactation and key opportunities to accelerate generation of high-quality evidence for improved maternal and perinatal health.]