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Understanding pregnancy: Accelerating the development of new therapies for pregnancy-specific conditions

25 September 2023

Academy of Medical Sciences' FORUM workshop, held in partnership with Birmingham Health Partners and the Concept Foundation

Concept Foundation

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The Academy of Medical Sciences' FORUM provides an independent platform for senior leaders from across academia, the commercial sector, government, and the charity, healthcare and regulatory sectors to come together with patients and take forward national discussions on scientific opportunities, technology trends and associated strategic choices for healthcare and other life sciences sectors.

Opinions expressed in this report do not necessarily represent the views of all participants at the event, the Academy of Medical Sciences, or its Fellows.

All web references were accessed in February 2024.

Understanding pregnancy: Accelerating the development of new therapies for pregnancy-specific conditions

FORUM workshop on Monday 25 September 2023

Jointly hosted by the Academy of Medical Sciences, Birmingham Health Partners and the Concept Foundation

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Executive summary

During pregnancy, women and pregnant individuals who do not identify as women[1] can develop a range of pregnancy-specific conditions, such as pre-eclampsia and gestational diabetes, that can adversely affect both their own health and that of the developing fetus during the pregnancy. These conditions can affect the lifelong health of both mother and child. Despite the danger that these conditions present to mother and baby, there are few approved, safe and effective medicines to treat them, and limited investment in novel therapy development.

The lack of safe and effective medicines for pregnancy-specific conditions reflects significant challenges along the entire drug discovery and development pathway, which includes the need to minimise the risk to both women and their unborn babies in research studies and clinical trials. These challenges complicate preclinical research into the physiology of healthy pregnancy, the mechanisms of disease of pregnancy-specific conditions, and potential therapeutic interventions. Preclinical evidence is essential for identifying candidate treatments for pregnancy-specific conditions and for designing clinical trials to test their safety and efficacy.

To map out key barriers and potential enablers of preclinical research and experimental medicine to support the development of new medicines for pregnancy-specific conditions, the Academy of Medical Sciences, Birmingham Health Partners, and Concept Foundation organised a multi-sectoral FORUM workshop in September 2023. People with lived experience joined representatives from academia, the commercial sector, clinical practice (including doctors and midwives), regulatory authorities, funding bodies, charities, and patient advocacy groups at the meeting.

Participants highlighted that stimulating more early-stage research on pregnancy-specific conditions could improve understanding of disease mechanisms, identify new targets for medicine development, and develop methods for better evaluating safety, toxicity, and dosage prior to early-stage clinical trials. Such advances could invigorate medicine development for pregnancy-specific conditions and drive renewed commercial interest in the development of treatments. The workshop did not focus on the specific challenges of running clinical trials in pregnancy; however, participants discussed the need for evidence from preclinical research and experimental medicine to support the design and approval of clinical trials for candidate medicines for pregnancy-specific conditions, and inform recruitment of trial participants.

Participants proposed next steps (outlined in the report) around the following priorities:

1. **A cross-sectoral and cross-speciality network or coalition, including women with lived experience, to provide a platform for collaboration and to coordinate efforts to promote the development of new medicines for pregnancy-specific conditions.**
2. **Additional interdisciplinary research and cross-sector collaboration to address key knowledge gaps (including the biology of the placenta, of the early stages of pregnancy, and of pregnancy-specific conditions), to enable appropriate use of**

[1] The Academy acknowledges that not all pregnant people identify as women. While the terms 'woman' and 'mother' are used here, many of the learnings from the workshop about obstetric/pregnancy-specific conditions are expected to be widely applicable. It is recognised that there will be specific experiences and challenges associated with obstetric conditions among pregnant individuals who do not identify as women that were not explored at the workshop given the lack of specific research in this area.

animal models and physiologically based pharmacokinetic (PBPK) modelling, and to leverage routinely collected health data and patient samples. Combining preclinical data from different research tools, including multiple species, could provide a powerful approach to overcome the limitations presented by any individual model for the study of pregnancy. Access to human tissue for this research is essential as many features of human pregnancy and pregnancy-specific conditions are not present in animals. However, most biological samples from pregnant women are from healthy, late-stage pregnancies. To enable pregnancy research, participants proposed the establishment of a biobank that collects biological samples linked with relevant health data from pregnant women, including those with pregnancy-specific conditions. Participants also noted that linking the health data of mother and child is important (e.g. for research into the long-term impacts of pregnancy-specific conditions and their treatments).

3. **The establishment of a more enabling environment for research in pregnancy, for example through development of a stronger research base and a more supportive regulatory environment.** The additional regulatory challenges for proving safety of medicines for both the pregnant woman and the fetus using traditional approaches and experimental models have acted as a deterrent to commercial investment. Given the diversity of novel tools being developed for pregnancy research, participants suggested a cross-sector workshop to explore the regulatory acceptability of novel experimental models. Participants also highlighted that research into pregnancy-related conditions, and women's health more generally, is underfunded, which affects the sustainability of the workforce, and should be seen as a greater public health priority.
4. **Greater engagement with women to raise awareness of the importance of research into pregnancy and of opportunities to participate in this research,** including when women contact the healthcare system. Such opportunities could include blood/tissue donation, allowing access to health records for research, and participation in interventional studies. Participants felt that the opportunity to participate in research should be a routine part of care of pregnant women, whilst ensuring that such opportunities are presented sensitively. Participants strongly felt that efforts are needed to ensure equitable opportunity for research participation (for example, by working with community-based organisations to build trust and engage underserved communities).
5. **Education and training of healthcare professionals, including midwives, to promote research in pregnancy.** Healthcare professionals often do not encourage women, particularly pregnant women, to participate in research, perhaps due to perceived risk and/or lack of awareness of potential benefits. Participants proposed a survey of attitudes of healthcare professionals to pregnancy research to explore the reason for any reluctance. Informed by the results, participants suggested the Royal Colleges would be well placed to facilitate relevant education and training.
6. **Advocacy to secure greater prioritisation of research in pregnancy (and women's health more generally) by policymakers, funders, and higher education institutions.** As well as highlighting disease burdens, medical needs and long-term impacts (economic as well as health), participants suggested that advocacy strategies should develop strong positive messaging, including by highlighting evidence-based success stories (e.g. Annex 3).

There was a strong appetite amongst participants to maintain momentum and continue the cross-sector conversations begun at the workshop. Greater prioritisation of research in pregnancy, increased funding, and dialogue with regulatory authorities could reshape the landscape for research in pregnancy and promote translation of research findings into much-needed treatments for pregnancy-specific conditions.

Introduction

During pregnancy, women and pregnant individuals who do not identify as women[2] can develop a range of serious health conditions. These include pre-eclampsia and gestational hypertension (high blood pressure), gestational diabetes, intrahepatic cholestasis of pregnancy (reduced or stalled bile flow from the liver), and hyperemesis gravidarum (severe and persistent vomiting). Pregnancy-specific conditions can also affect the health of babies, for example by restricting fetal growth or by leading to premature birth or stillbirth. In addition, pregnancy and pregnancy-specific conditions can affect the long-term health of women and their children, increasing the risk of other health conditions. Pregnancy-specific conditions are common: every year, approximately 130,000 births in the UK, and 20 million births globally, are preterm (or premature) and/or affected by hypertension, pre-eclampsia, or intrahepatic cholestasis of pregnancy.[3]

There are few safe and effective medicines for pregnancy-specific conditions. This reflects significant challenges along the entire drug discovery and development pathway, including the need to minimise the risk to both women and their unborn babies in research studies and clinical trials. These challenges complicate preclinical research into the physiology of healthy pregnancy, the mechanisms of disease of pregnancy-specific conditions, and potential therapeutic interventions, and add to the complexity of running clinical trials of candidate treatments. The need to consider the developing fetus as well as the pregnant woman herself also often makes meeting regulatory requirements particularly challenging for any medicine used in pregnancy, including those for pregnancy-specific conditions. For novel medicines for pregnancy-specific conditions, there is the added challenge that it is often not possible to conduct safety and efficacy studies in healthy, non-pregnant people. In addition, there is strong financial and reputational risk for developers if a candidate medicine does not perform as expected in a trial and leads to harm.

Although not directly a focus of the workshop, clinical trials for pregnancy-specific conditions often have added considerations and complexities. For example, extensive monitoring of both mother and fetus is essential, during and beyond a trial. Ideally, long-term impacts on development after birth would be assessed, but these can be costly and difficult to follow-up. Obtaining insurance for clinical trials can also be difficult, as risks are hard to assess due to the relative rarity of trials of medicines in pregnancy.

All these factors collectively discourage commercial investment in therapy development for pregnancy-specific conditions. As a result, the treatment pipeline for pregnancy-specific conditions is poorly stocked.

One way to generate new translational opportunities would be to stimulate more early-stage research on pregnancy-specific conditions, in order to improve understanding of disease mechanisms, identify new targets for medicine development, and develop methods for better evaluating safety, toxicity, and dosage prior to early-stage clinical trials. These advances could

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[3] King's College London (2022). *Improving outcomes of high-risk pregnancy.* https://www.kcl.ac.uk/news/spotlight/improving-outcomes-of-high-risk-pregnancy

create new opportunities and drive renewed commercial interest in the development of treatments for pregnancy-specific conditions.

In response to the need for new medicines for pregnancy-specific conditions, Concept Foundation recently launched the Accelerating Innovation for Mothers initiative,[4] which aims to foster global partnerships to accelerate the development and introduction of new treatments for pregnancy-specific conditions. In addition, in 2022, Birmingham Health Partners published a report, 'Healthy mum, healthy baby, healthy future',[5] which made several recommendations to stimulate cross-sector working and position the UK as a global leader in developing safe, effective, and accessible medicines for use in pregnancy, and called for greater efforts to incentivise commercial investment in this area. The Academy of Medical Sciences' previous work on women's health has also drawn attention to the relative lack of research into pregnancy-specific conditions.[6]

Against this backdrop, on 25 September 2023, the Academy of Medical Sciences, Concept Foundation and Birmingham Health Partners organised a cross-sectoral FORUM workshop to explore the barriers to medicine development for pregnancy-specific conditions. The workshop focused on the preclinical stages of medicine development – the development of new therapies up to the point at which they are evaluated in clinical trials. Participants included individuals from academia, clinical practice (including doctors, midwives etc), the commercial sector, and the regulatory sector, as well as people with lived experience. They considered key challenges and practical steps that could be taken to advance preclinical research on pregnancy-specific conditions to facilitate new therapy development. In particular, participants discussed:

- Research priorities, opportunities, and challenges in pregnancy research, in relation to the preclinical space, experimental medicine, and the use of health data.
- Tools and assays to model medicine efficacy, mechanism of action, toxicity, and pharmacokinetic and pharmacodynamic properties (of the mother and fetus/neonate) in pregnancy.
- The role of a research-enabled healthcare system to enable preclinical pregnancy research and experimental medicine, to provide access to patient samples with sufficient joined-up data, and to improve recruitment through trust and communication.

As preclinical research is shaped by the requirements of clinical stages of medicine development and the policies of regulatory authorities, participants also touched upon issues relating to experimental medicine studies and clinical trials.

The workshop was chaired by **Professor Peter Brocklehurst** FMedSci, Emeritus Professor of Women's Health at the University of Birmingham, and **Dr Pauline Williams** CBE FMedSci, an independent pharmaceutical medicine consultant and former Senior Vice-President and Head of Global Health R&D at GlaxoSmithKline. The workshop agenda, participant list and a glossary can be found in Annex 1, Annex 2, and Annex 4, respectively.

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[4] https://www.conceptfoundation.org/accelerating-innovation-for-mothers/
[5] Birmingham Health Partners (2022). *Healthy mum, healthy baby, healthy future: The case for UK leadership in the development of safe, effective and accessible medicines for use in pregnancy*. 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
[6] Academy of Medical Sciences (2021). *Women's health: A life-course approach.* https://acmedsci.ac.uk/more/events/womens-health-a-life-course-approach

Challenges developing medicines for pregnancy-specific conditions

Pregnancy-specific conditions, such as pre-eclampsia and gestational diabetes, adversely affect both the health of the mother and that of the developing fetus during pregnancy, often with impacts felt throughout the life of both. Despite this, there are few medicines approved to treat pregnancy-specific conditions and many challenges for the development of new therapies. In the scene-setting talks at the workshop, speakers reflected on their personal and professional experiences tackling pregnancy-specific conditions.

The personal impact of a pregnancy-specific condition

Pregnancy-specific conditions affect large numbers of women and their children each year; for example, approximately 10,000 to 30,000 women per year experience hyperemesis gravidarum (HG; extreme vomiting during pregnancy). However, there are few, and in some cases no, treatments for these conditions. The negative impact on the health and wellbeing of women and their children represents a significant unmet need. **Dr Caitlin Dean**, spokesperson for the charity Pregnancy Sickness Support, discussed her debilitating experience of hyperemesis during pregnancy, illustrating why new medicines are so urgently needed. Her experience also raises questions about the attitudes of some health professionals to medicines use during pregnancy, a potential barrier to the use of newly developed medicines.

While occasional nausea and vomiting is common in early pregnancy, Dr Dean was diagnosed with hyperemesis gravidarum (HG), characterised by excessive nausea and extreme vomiting, which often results in dehydration and severe and rapid weight loss. One in five of women experiencing HG in the UK each year will experience symptoms throughout their pregnancy.[7]

Dr Dean experienced HG during all three of her pregnancies. The condition was not managed effectively in her first two pregnancies. This was partly due to the reluctance of some GPs that she interacted with at the time to prescribe medications to control her symptoms, due to concerns about possible side effects on her baby. The uncontrolled symptoms had a significant impact on her quality of life, leading to weight loss and hospitalisation, and affecting her own health as well as risking the health of her unborn child. Her symptoms were, however, effectively managed – though not eliminated – using medication during her third pregnancy.

Driven by her experiences, Dr Dean set up a charity (Pregnancy Sickness Support) and helpline, and now advocates for better support for women suffering severe sickness during pregnancy. She also works to raise awareness among healthcare professionals. At the workshop, she emphasised that new research was needed to generate evidence and understanding to support the development of treatments for a condition that, without treatment, can have a devastating impact and in certain circumstances can lead to the termination of pregnancies.

[7] https://www.pregnancysicknesssupport.org.uk/get-help/what-is-hyperemesis-gravidarum/

The challenges facing medicine development for pregnancy-specific conditions

There are many reasons for the lack of treatments for pregnancy-specific conditions, including cultural perceptions of medicating women during pregnancy, gaps in the understanding of the biology of pregnancy and pregnancy-specific conditions, and regulatory challenges. **Dr Allyah Abbas-Hanif**, Consultant in Pharmaceutical Medicine and GP, Chair of the Faculty of Pharmaceutical Medicine's Paediatric and Women's Health Expert Group, and Honorary Senior Clinical Lecturer at Imperial College London, outlined key challenges facing those developing new medicines for pregnancy-specific conditions.

Pregnant women are an underserved population: only two medicines – atosiban and carbetocin – have been developed specifically for pregnant women in the past 40 years. Dr Abbas-Hanif noted that the field was heavily influenced by thalidomide use in the 1950s. Thalidomide was marketed as an anti-emetic to treat morning sickness, based on insufficient evidence from preclinical and animal models,[8] and was then found to affect prenatal development, causing birth defects. The desire to avoid a repeat of this scenario led to the development of modern-day pharmacovigilance systems. However, fears of harm have led to the strong reluctance to expose women of childbearing age to appropriate experimental medicines or clinical trials, limiting medicines development and access.

Thalidomide illustrated the need for rigorous preclinical assessment of the potential impacts of candidate treatments on fetal development. Fetal defects with thalidomide occur when given before birth in many model species, but not mice, a commonly used animal model. The placenta, which plays an active role in controlling the transfer of metabolites and medicines from mother to fetus, also varies in function between animal species. The limitations of individual species used as animal models led to the regulatory requirement for evidence from multiple species as well as laboratory tests to be gathered during early phases of medicine development. Rigorously defined developmental and reproductive toxicology (DART) requirements were introduced to ensure the safety of candidate medicines for pregnant women, based on thorough testing in animals. To ensure global consistency, guidance on DART studies is provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[9] The ICH is developing a new Efficacy Guideline on the 'Inclusion of Pregnant and Breastfeeding Individuals in Clinical Trials' to provide a globally accepted framework and best practice.

Physiological changes during pregnancy affect the metabolism of drugs, influencing circulating drug levels, fetal exposures, and drug susceptibility. Because direct sampling is challenging, physiologically based pharmacokinetic modelling is an important tool for assessing drug levels in different tissues, for informing dosing, and for providing estimates of likely fetal exposure to drugs.

Dr Abbas-Hanif concluded that those interested in developing medicines for pregnancy-specific conditions should develop a clear understanding of the biological mechanism of the disease, drug targets, and possible risks associated with interfering with their function based on preclinical data from multiple species, to identify potential hazards and help develop appropriate risk mitigation strategies for clinical trials. Desirable features of an experimental medicine include minimal off-target effects and a large safety margin in preclinical studies. She also

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[8] A model system is an animal or experimental set-up designed for the study of specific biological processes, often to gain insight into how that process might happen in humans.
[9] ICH (2020). *ICH S5 (R3) Detection of developmental and reproductive toxicity for human pharmaceuticals.* https://database.ich.org/sites/default/files/S5-R3_Step_4_Presentation_2020_0222_0.pdf

recommended engaging early and frequently with regulators to ensure a good understanding of regulatory requirements and data needs from preclinical studies in advance of clinical trials. Other activities that could enhance translation include the development of target product profiles (TPPs) for medicines for pregnancy-specific conditions as a guide to be used by product developers.

Translation from idea to clinical trial – a perspective from academia

Novel concepts for the treatment of pregnancy-specific conditions often come from scientific discoveries made during the course of academic research. However, the process of gathering enough evidence about the safety and efficacy of these potential treatments to get approval to conduct a clinical trial in humans is long and challenging. **Professor Anna David**, Director of the UCL Institute for Women's Health and Professor and Consultant in Obstetrics and Maternal Fetal Medicine at University College London, described her own experience as a researcher in academia developing an innovative gene therapy for fetal growth restriction – when the growth of a fetus is abnormally slow or stops completely.

Fetal growth restriction is caused by impaired development of the placenta, which is unable to ensure a sufficient supply of nutrients to support healthy growth of the developing fetus. This can lead to stillbirth, preterm birth, or birth of babies abnormally small for their gestational age, who are at risk of immediate and long-term threats to health. In 2005, Professor David developed the idea of using maternal gene therapy to enhance production of a specific growth factor, known as VEGF (vascular endothelial growth factor), to improve the function of the placental blood supply in affected pregnancies. To test this idea, she studied the effects and effectiveness of the therapy in pregnant sheep, a commonly used model in reproductive health,[10,11,12] and in a novel pregnant guinea pig model of the condition, which needed to be developed for the purpose.[13]

To progress towards clinical application, Professor David conducted a range of further studies,[14] including tests on human placental tissue,[15] DART studies, and exploration of bioethical issues.[16] The programme also included an observational cohort study to better document the course of condition and to identify the most appropriate clinical population to enrol in a trial (those with the most severe symptoms).

The rarity of medicine trials in pregnant women meant that development of a protocol for a planned clinical trial was particularly complex. Extensive bioethical analyses and patient consultations were undertaken, which confirmed the acceptability of the approach and the willingness of women to participate in trials. A refined set of safety criteria had to be developed.[17] Other important spinoffs have included the first orphan disease designation[18] for

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[10] David AL, *et al*. (2008). *Local delivery of VEGF adenovirus to the uterine artery increases vasorelaxation and uterine blood flow in the pregnant sheep.* Gene Ther. **15(19),** 1344–50.
[11] Carr DJ, *et al*. (2014*). Uteroplacental adenovirus vascular endothelial growth factor gene therapy increases fetal growth velocity in growth-restricted sheep pregnancies.* Hum Gene Ther. **25(4)**, 375–84.
[12] Carr DJ, *et al*. (2016). *Peri- and postnatal effects of prenatal adenoviral VEGF gene therapy in growth-restricted sheep.* Biol Reprod. **94(6)**, 142.
[13] Swanson AM, *et al*. (2016). *Maternal therapy with Ad.VEGF-A_{165} increases fetal weight at term in a guinea-pig model of fetal growth restriction.* Hum Gene Ther. **27(12)**, 997–1007.
[14] Spencer R, et al. (2017). *EVERREST prospective study: a 6-year prospective study to define the clinical and biological characteristics of pregnancies affected by severe early onset fetal growth restriction.* BMC Pregnancy Childbirth **17(1),** 43.
[15] Desforges M, *et al.* (2018). *In vitro human placental studies to support adenovirus-mediated VEGF-$D^{\Delta N \Delta C}$ maternal gene therapy for the treatment of severe early-onset fetal growth restriction.* Hum Gene Ther Clin Dev. **29(1),** 10–23.
[16] Sheppard M, *et al.* (2016). *Ethics and social acceptability of a proposed clinical trial using maternal gene therapy to treat severe early-onset fetal growth restriction.* Ultrasound Obstet Gynecol. **47(4),** 484–91.
[17] Spencer RN, *et al*. (2022). *Development of standard definitions and grading for Maternal and Fetal Adverse Event Terminology.* Prenat Diagn. **42(1)**, 15–26.

fetal growth restriction,[19] new prognostic indicators for pregnancy outcomes following diagnosis,[20] a better understanding of the impact of the disease on neonatal outcome,[21] and economic analyses of the impact of early-onset fetal growth restriction, which suggest that each case incurs short-term care costs of around £100,000 from diagnosis to neonatal discharge.[22]

Material for clinical trials has been manufactured and is being retested for safety and effectiveness, in advance of trials planned to start in 2025. The experience highlights the long timeframes typical of new medicine development for pregnancy-related conditions – after an initial discovery in 2005, a first-in-human trial is due to take place 20 years later; clinical trials could take at least another decade, with no guarantee of success. Frequent dialogue with regulatory agencies, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA), has been essential, in order to ensure that preclinical studies deliver the evidence required for regulatory approval of an application to begin human studies. Collaboration with other sectors has also been important to this work, including extensive consultation with pregnant women, partnership with a pharmaceutical company, and funding from a variety of sources, both in the UK and beyond. Professor David suggested that pregnancy-specific conditions are an untapped market for pharmaceutical companies, if the challenges involved can be overcome.

In conclusion, Professor David noted the importance of developing a good understanding of the clinical population and clinical outcomes, in order to identify appropriate patient populations and outcome measures for trials. In her experience, patients are willing to participate in research.

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[18] Drugs with orphan disease designation are intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating and affects not more than 5 in 10000 people in Great Britain (or the drug would not deliver return on investment). For more information: https://www.gov.uk/guidance/orphan-medicinal-products-in-great-britain

[19] Spencer R, *et al.* (2018). *Achieving orphan designation for placental insufficiency: annual incidence estimations in Europe*. BJOG **126**, 1157–67.

[20] Spencer R, *et al.* (2023). *Maternal PlGF and umbilical Dopplers predict pregnancy outcomes at diagnosis of early-onset fetal growth restriction*. J Clin Invest **133(18)**.

[21] Lingam I, *et al.* (2023). *Neonatal outcomes following early fetal growth restriction: a subgroup analysis of the EVERREST study.* Arch Dis Child Fetal Neonatal Ed **108(6)**, 599–606.

[22] Bray G, *et al.* on behalf of EVERREST consortium. (2022). *The economic cost of severe early-onset fetal growth restriction.* British Maternal Fetal Medicine Conference Birmingham. BJOG **130(S1)**, 88.

Identifying ways forward and developing a future agenda

Advancing preclinical research to develop treatments for pregnancy-specific conditions is a cross-sector challenge. Panellists from different sectors discussed the challenges and opportunities for different stakeholder groups in a panel discussion after the scene-setting talks.

Panellists agreed that it is vitally important to engage women in research into pregnancy and pregnancy-specific conditions, both in terms of participating in research studies and being involved in the prioritisation and design of research studies. **Dr Clea Harmer**, Chief Executive of the Stillbirth and Neonatal Death Charity (Sands), which supports those affected by the death of a baby and works to reduce the numbers of such deaths, acknowledged that approaching women at an emotionally charged time is inevitably difficult, but highlighted that many pregnancy-specific conditions recur in future pregnancies, so women have a strong interest in research aiming to improve pregnancy outcomes. Dr Harmer also noted that some women who have been affected by the death of a baby may find solace and comfort in being involved in research, and the thought that others will benefit from their contributions.

Marcus Green, Chief Executive of Action on Pre-eclampsia, highlighted that pregnancy-specific conditions can have long-lasting impacts and affect the life-long health of women and their babies. For example, those with high blood pressure or diabetes during pregnancy have increased risk of recurrence of these conditions later in life. Therefore, women often have a personal interest in research to better understand and address such conditions.

Mr Green further emphasised that work in this field is often siloed, and that more could be achieved if different groups worked with each other more effectively. He suggested that the voluntary sector could bring important benefits to collaborative partnerships, including greater access to key groups such as politicians.

For any medicines used during pregnancy, medicine developers and regulators must consider both their safety and efficacy in women and their possible effects on the growing fetus. Moreover, **Dr Janet Nooney**, Expert Scientific Assessor at the MHRA, highlighted that medicine development for pregnancy-specific conditions comes with additional regulatory challenges. For medicines for general uses, it may be possible to gain some general information about safety and efficacy in humans using data from a non-pregnant population before studying their effect in pregnant women. But for medicines for pregnancy-specific conditions, safety and efficacy must be primarily established in pregnant women. In some cases, it might be possible to refer to data from a non-pregnant population with a comparable condition. However, it may not be clear whether the disease mechanism is sufficiently similar to make a valid comparison (e.g. pre-eclampsia and hypertension), so further data may be needed, especially for drugs with a novel mechanism of action. Further challenges include the limitations of tools to model pregnancy and pregnancy-specific conditions. For example, physiologically based pharmacokinetic modelling is a vital tool, but Dr Nooney noted that such modelling is typically based on data from healthy pregnancies, and applicability of existing models to different pregnancy-related conditions is uncertain and may be limited in some cases.

Existing animal models of pregnancy-specific conditions also have limitations as models to test candidate medicines, given that such conditions do not naturally occur in animals. This raises uncertainty about how well therapies will translate from animals to humans. **Dr Edith Roset Bahmanyar**, Executive Director (Clinical Research and Development) at Organon, a

pharmaceutical company specialising in women's health, noted increasing opportunities to engineer new animal models, when specific disease-causing mechanisms have been identified. However, limited understanding of disease processes often remains a major barrier to model development. Furthermore, developing a new animal model is time-consuming and requires validation by regulators, which can delay the time to market for a medicine developer. As Dr Nooney pointed out, regulators must have confidence that effects seen in animal models are also likely to be seen in humans, and that the results of modelling studies are reliable.

Dr Roset Bahmanyar mentioned that medicine development for pregnancy-specific conditions faces additional specific challenges, including a lack of understanding of pathophysiology (e.g. for pre-eclampsia and preterm birth), and the difficulty of conducting trials in pregnant women. For example, once a molecule is expected to have the right mechanism of action, establishing the therapeutic dose level that is likely to be efficacious but also safe for both mother and child is a major challenge, and has to be estimated using modelling with a significant margin of uncertainty. It is also important to consider the timing of treatment, given the varying susceptibility of an embryo or fetus at different developmental stages. Different compounds vary significantly in their ability to cross the human placenta, adding further uncertainty. Dr Roset Bahmanyar noted that these complexities and uncertainties come with risk of long-term fetal harm and a high risk of medicine failure, tempering the interest of pharmaceutical companies in the area. Developing a deeper understanding of maternal diseases, establishing pharmacology standards for pregnancy, and guidance from regulatory authorities are therefore critical aspects of new medicines development for pregnancy-specific conditions.

As noted by **Professor Catherine Williamson** FMedSci, Professor of Women's Health at Imperial College London, pregnancy-specific conditions are typically complex and multifactorial, influenced by both biological and socio-environmental risk factors. A condition may have multiple causes, and a treatment may only be effective for a subset of patients with a particular condition. This argues for the importance of clinical characterisation of patient groups to support patient stratification, for inclusion in trials and for targeting and timing of treatments in clinical practice. Research into disease mechanisms and clinical progression can help to identify biomarkers, molecules that show an association with risk of disease and/or disease progression. Biomarkers may have clinical utility in risk prediction and patient stratification, guiding patient care and identification of suitable participants for clinical trials.

A wide range of tools and technologies can now be applied in research into pregnancy-specific conditions, and Professor Williamson emphasised the importance of interdisciplinary research collaborations to provide a more integrated picture of diseases in pregnancy. These can combine clinical outcomes data with results from physiological, 'omics',[23] and other studies on patient samples, and data from animal models, to identify new targets for therapy development and biomarkers for patient stratification.

As well as discovery and development of entirely new therapies, it may also be possible to reuse existing medicines – known as drug repurposing. A deeper understanding of mechanistic causes of disease may suggest that an existing medicine has the potential to interfere with disease processes or correct a deficiency, which can then be tested in animal models of disease in addition to robustly designed clinical trials.

Furthermore, panellists agreed that evidence-based success stories of research and medicine development for pregnancy should be better communicated to stimulate more research interest

[23] 'Omics' is a term often used as shorthand for large-scale analysis of multiple biological molecules, such as messenger RNA molecules (transcriptomics), proteins (proteomics), lipids (lipodomics) or other metabolites (metabolomics).

in this area of medicine. One example is the effective research collaboration studying intrahepatic cholestasis of pregnancy (reduced or stalled bile flow from the liver), which has led to the use of blood tests to predict which pregnancies are at risk of stillbirth or preterm birth,[24] a medicine to reduce the risk of spontaneous preterm birth (ursodeoxycholic acid, UDCA),[25] two further medicines in clinical trials, and genomic screening,[26] which has been adopted by the NHS genomic medicine service. Another example is the significant advance in the understanding of the mechanism underpinning HG, announced since the workshop and described in Annex 3,[27] which demonstrates the value of an interdisciplinary approach, as highlighted by Professor Williamson and others at the workshop.

As noted by Dr Roset Bahmanyar, medicine development for pregnancy-specific conditions is not currently seen as an attractive proposition for the commercial sector, and a focus in this area often only occurs when senior commercial leaders are personally motivated and prepared to take on additional risk. It was suggested that mechanisms are needed to incentivise commercial investment and to de-risk early development. Possible actions for developers could be collaborations with academia to improve understanding of potential targets and the effects of interfering with their function, and early dialogue with regulators, to ensure clarity on data requirements. The MHRA and EMA both offer a scientific advice services.[28] [29]

To build a pipeline of new treatments for pregnancy-specific conditions, panellists and participants agreed that novel therapeutic strategies need to be identified and explored, based on a more comprehensive understanding of disease mechanisms. This is likely to require concerted action across a range of stakeholders. The key priorities identified during discussions are listed below.

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[24] Ovadia C, *et al.* (2019). *Adverse perinatal outcomes of intrahepatic cholestasis of pregnancy and association with biochemical markers: results of aggregate and independent patient data meta-analyses.* Lancet **393 (10174),** 899–909.
[25] Ovadia C, *et al.* (2021). *Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: an individual patient data meta-analysis.* Lancet Gastro Hep **6(7)**, 547–58.
[26] Turro E, *et al.* (2020). *Whole-genome sequencing of patients with rare diseases in a national health system.* Nature **583(7814)**, 96–102.
[27] Note that the findings described in Annex 3 were published after the workshop took place and were not explicitly discussed by workshop participants, though organisations represented at the workshop were involved in the work.
[28] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra; Requests can be sent to scientific_advice@mhra.gov.uk
[29] https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-advice-and-protocol-assistance

1. A cross-sectoral and cross-speciality network or coalition, including women with lived experience, to provide a platform for collaboration and to coordinate efforts to promote the development of new medicines for pregnancy-specific conditions

Participants recognised the need for key stakeholders – academia, the commercial sector, the healthcare sector, research charities, regulators, and people with lived experience – to work together to accelerate the development of new medicines for pregnancy-specific conditions. Each sector has its own individual strengths, but all also faces sector-specific challenges. By joining forces, the sectors can collaborate more effectively, share knowledge and align their activities.

Academia is crucial for advancing understanding of the physiological mechanisms of pregnancy and how they are altered in pregnancy-specific conditions. It can also identify potential targets and generate promising therapeutic leads. Participants suggested widening existing maternity research networks and linking them up with each other and other research networks, such as primary care research networks. The commercial sector is best placed to take novel therapeutic leads through the medicine development process, secure licensing approvals and establish quality manufacturing systems. The commercial sector may also be able to provide academic researchers with additional resources, such as preclinical models and candidate medicines. However, participants noted that, currently, academia and the commercial sector are not well connected within this field. Bringing together these groups (along with others such as women with lived experience and charities – see below) and incentivising collaboration could lead to productive cross-fertilisation, enabling identification of the most promising leads and addressing key gaps in knowledge to help progress candidate treatments. Increased dialogue could help academic researchers better understand how their research could have practical applications. For commercial medicine developers, as well as identifying potential new leads, early engagement in this field through academic collaborations could help to de-risk medicine development and encourage investment by providing additional data on the biological activities and safety profile of promising compounds.

As highlighted by Professor Williamson in the panel discussions, interdisciplinary research collaborations are critical, given the potential for multiple different technologies to be applied to understand complex disease processes. In addition, there was felt to be a need for a systems-based approach to better understand interactions between the mother, placenta, and fetus. It was also noted that, as well as pregnancy-specific medicines, a deeper understanding of the basic physiology of pregnancy would advance multiple other areas of medicine, including oncology and reproductive health.

Given their role in approving therapies and clinical study protocols, participants, speakers and panellists strongly emphasised the importance of engaging regulators early on in the process of exploring therapies for pregnancy-specific conditions, to help ensure evidence requirements to demonstrate safety and efficacy are understood and satisfied. Given the potential for increased litigation risk when conducting research studies in pregnant women, participants noted that the involvement of individuals with relevant legal expertise in collaborations would also be useful.

Participants stressed the benefits of including women with lived experience, patient advocacy groups, and relevant charities within collaborations. These organisations can facilitate the involvement of women in research (for example, to ensure that research addresses women's priorities) and promote recruitment into research studies. They also offer a compelling voice to advocate for pregnant women and those with pregnancy-specific conditions with policymakers (see sixth point below).

A joined-up approach could facilitate the development of a common set of messages to advocate for prioritisation of work in this area with other stakeholders, such as policymakers and politicians, funding agencies, and regulatory authorities. Developing such messages might involve defining key research questions and building consensus about infrastructure needed to advance the field (e.g. in terms of policy, funding, and regulation).

Participants suggested that this focal point for the field could be a new network, a virtual platform providing opportunities to collaborate, or an informal coalition or alliance of interested parties.

Next steps proposed by participants:

1.1. Establishing a cross-sectoral and multidisciplinary network or coalition to provide a focal point for R&D in pregnancy and a single voice to advance the field. In particular, a joint 'mission' (akin to others proposed through the Life Sciences Vision and currently successfully operating, such as the Mental Health Mission) to develop medicines for pregnancy-specific conditions would be useful. Existing research networks could be used as the basis for this.

1.2. Organising a cross-sectoral initiative to review of the current state of play in drug discovery and development for the most common pregnancy-specific conditions.

2. Additional interdisciplinary research and cross-sector collaboration to address key knowledge gaps (including the biology of the placenta, of the early stages of pregnancy, and of pregnancy-specific conditions), to enable appropriate use of animal models and physiologically based pharmacokinetic (PBPK) modelling, and to leverage routinely collected health data and patient samples

Participants suggested that there were many gaps in knowledge, relating to both the basic physiology of pregnancy and the pathophysiology of pregnancy-specific conditions (such as what causes a disease, the trajectory of the disease, the underlying mechanisms, and the impact of the disease on the system). A wide range of research tools is now available to explore physiological function, including various 'omics' technologies,[30] advanced imaging,[31] and targeted genetic modifications, applicable to a variety of different experimental models, from animal models (*in vivo*), to the study of specific tissues outside the body (*ex vivo*), to the study of specific cells or groups of cells outside the body (*in vitro*). An interdisciplinary approach offers great potential to apply this diversity of tools to generate a more complete and integrated view of healthy pregnancy and pregnancy-specific conditions. Participants suggested that the combination and integration of data from the models available, perhaps with the help of artificial intelligence, could provide a powerful approach to overcome the limitations presented by any individual model for studying pregnancy and pregnancy-specific conditions.

[30] 'Omics' is a term often used as shorthand for large-scale analysis of multiple biological molecules, such as messenger RNA molecules (transcriptomics), proteins (proteomics), lipids (lipodomics) or other metabolites (metabolomics).
[31] Clark A, *et al.* (2023). *Developments in functional imaging of the placenta.* Br J Radiol. **96(1147)**.

Placental physiology

The physiology of the placenta was felt by participants to be poorly understood. It has a significant role to play in controlling access of molecules in the blood, including drugs and metabolic products, to the fetus. Far from being a simple sieve, the placenta has active transporter mechanisms that regulate the movement of materials. Moreover, as fetal growth restriction illustrates, the function of the placenta is critical to fetal development and can be viewed as a key biological system regulating the exposure of the fetus to medicines, with the potential to be harnessed for treatment of the fetus. However, factors affecting how different compounds cross the placenta are incompletely understood, and current modelling is predominantly based on the healthy placenta rather than the placenta in a disease state.

Participants suggested that understanding the mechanisms of cross-placental transfer could facilitate the development of medicines that do not cross the placenta, enabling them to be taken by the mother safely during pregnancy without concern for possible impacts on the fetus. One example is certolizumab, a medication used to treat inflammatory conditions such as rheumatoid arthritis. Unlike some other antibody-based medications,[32] certolizumab lacks structures that facilitate transfer across the placenta, protecting the fetus from exposure to a medicine that might interfere with its development, so it is safe to be used during pregnancy.[33] The design of medicines could therefore be informed by an understanding of the structural features associated with cross-placental transfer.

One limitation of current approaches is that donated placental tissue generally comes from at-term, healthy pregnancies. Since placental physiology evolves over the course of a pregnancy, the development of the placenta has already peaked or begun to degenerate at the time of delivery. Limited material is available from pregnancies at earlier stages or from women affected by pregnancy-specific conditions (at any stage of pregnancy). The lack of biological samples makes it difficult to study the early stages of healthy pregnancy and the mechanisms underpinning pregnancy-specific conditions. One potential alternative source of placental tissue at earlier stages of pregnancy includes samples taken for tests for chromosomal disorders (such as Down's Syndrome). Some participants also suggested that engaging with women undergoing terminations could provide an alternative way to obtain biological material, including placental samples, at earlier stages of pregnancy. In addition, if these women have already been taking prescribed medications, analysis of such samples could generate data on transport of these medications across the placenta. Research would need to be done to explore the ethical considerations of using tissues from terminated pregnancies. It was strongly felt that it would be essential to carefully consider such requests and approach women and their families with sensitivity, given that this is often an emotionally difficult time for all involved. Consultation with women with lived experience would be required to determine the appetite for and acceptability of an offer to participate in research in this circumstance, and to help determine the most sensitive way to communicate the option. Some participants suggested that the opportunity to help to advance the development of treatments for conditions that arise during pregnancy might provide some comfort to women undergoing a termination.

In addition to using donated human placental tissue, there is interest in developing artificial placentas to study earlier stages of placental development. Three-dimensional placental organoids have been developed from trophoblast cells (cells in the embryo that provide

[32] Antibody-based medications either enlist or block the body's natural immune system. In the case of certolizumab, the antibodies block the activity of Tissue Necrosis Factor, a substance in the body that causes inflammation and leads to immune-system diseases such as rheumatoid arthritis.
[33] Mariette X, *et al.* (2018). *Lack of placental transfer of certolizumab pegol during pregnancy: results from CRIB, a prospective, postmarketing, pharmacokinetic study*. Ann Rheum Dis **77(2)**, 228–33.

nutrients and later develop into a large part of the placenta), providing a system for investigating placental function.[34,35] Other promising technologies to model the placenta include placental 'organ-on-a-chip' technology.[36] Unlike other mammalian-based models of placental function, such as sheep or guinea pig, these novel technologies have the advantage of being based on human cells, so in some ways they can better replicate the structure and function of the human placenta. Such artificial organs can also be used to screen large numbers of compounds to identify promising therapeutic medicine candidates. Methods used to develop these models can also be used to learn about other areas of pregnancy physiology in addition to placental physiology.

Human embryo models – embryos derived from human embryonic stem cells – offer new opportunities for understanding post-implantation embryonic development, although they also raise some significant ethical challenges.[37,38] This type of research is highly regulated. In the UK, by law human embryos grown in the lab can only be studied up to the equivalent of 14 days of development.

Animal models

A major theme of the meeting was the limitations of animal models of pregnancy-specific conditions. Animal models are central to research into disease processes and to assessment of the efficacy of novel interventions. An effective animal model for any disease should be as similar as possible to a human condition with respect to the question being asked in an experiment, to provide confidence that findings in animals are predictive of likely effects in humans. One issue for the study of pregnancy is that commonly used experimental animals, such as rodents, do not naturally experience some of the physiological processes and conditions seen in human pregnancy; pre-eclampsia, for example, has only been seen in primates. This has led to the development of new animal models, across numerous species, for the study of pregnancy-specific conditions, such as the guinea pig model of fetal growth restriction developed by Professor David. Regulators may be less familiar with these novel animal models and may need more evidence of their robustness before accepting them.

Participants noted that evidence from animal models is useful to answer particular questions about pregnancy, as long as the limitations of the specific models used are taken into account. Evidence from animal models is particularly powerful when data are compared and combined across different models and integrated with human data. In addition, advances in genetic manipulations are providing new opportunities to engineer more physiologically relevant animal models.

An additional use of animals is in safety testing, or developmental and reproductive toxicology (DART) studies. These seek to understand the effects of an investigational medicine on the fetus. The value of DART studies depends on how well the effects seen in an animal model predict those in humans. As there are significant differences in placental function in different types of animals, this has major implications for safety testing. Choice of animal model for safety testing is therefore crucial. For example, the effects of thalidomide on fetal development

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[34] Turco MY, *et al.* (2018). *Trophoblast organoids as a model for maternal-fetal interactions during human placentation.* Nature **564(7735)**, 263–7.
[35] Haider S, Beristain AG (2023). *Human organoid systems in modeling reproductive tissue development, function, and disease.* Hum Reprod **38(8),** 1449–63.
[36] Menon R, Richardson L (2022). *Organ-on-a-chip for perinatal biology experiments. Placenta* Reprod Med **1**, 98.
[37] Oldak B, *et al.* (2023). *Complete human day 14 post-implantation embryo models from naïve ES cells.* Nature **622**, 562–73.
[38] Weatherbee BAT, *et al.* (2023). *Pluripotent stem cell-derived model of the post-implantation human embryo.* Nature **622**, 584–93.

are not seen in rodents but are observable in animals such as rabbits, because of species-specific differences in metabolism of the drug.[39]

Physiologically based pharmacokinetic modelling

A further area identified by participants as critical to medicines development for pregnancy-related conditions was physiologically based pharmacokinetic (PBPK) modelling. Multiple physiological changes occur throughout pregnancy, including changes in the levels of enzymes that metabolise drugs. This may require dose adjustments to ensure that drug levels are sufficient to achieve a therapeutic effect. As experimental data may be limited, modelling approaches are generally needed to provide estimates of drug distributions within different organ systems or body compartments.

In addition, as sampling placental or fetal tissue is extremely difficult, PBPK modelling can be used to provide an estimate of drug concentrations within the placenta and in different compartments (such as the kidney or other organs) in the fetus. The EMA has published guidelines on the use of PBPK modelling in regulatory submissions, with strong input from MHRA assessors.[40] Further research is needed to refine these methods and their application across different stages of pregnancy and in different pregnancy-specific conditions.

Leveraging routinely collected health data and samples

Given the limitations of preclinical models of pregnancy and pregnancy-specific conditions, participants highlighted that clinical data from women during pregnancy could generate important insights to inform therapy development, prior to clinical trials. In particular, better use of routinely collected health data and patient samples was felt to offer opportunities to improve understanding of pregnancy and pregnancy-specific conditions. Participants suggested that studies could learn from and build on the ongoing efforts of Health Data Research UK (HDR-UK) and others, such as the MuM-PreDICT project,[41] which focuses on women with two or more long-term health conditions during pregnancy. Such projects could be leveraged to support treatment development, for example by extending their scope to include wider interdisciplinary collaborations and experimental studies in animal models.

Routinely collected patient samples, or material collected in observational cohort studies, can be a valuable resource for research, particularly when linked to health records. Participants proposed that research to generate a better understanding of the physiology of pregnancy including placental physiology could be facilitated by the creation of a biobank[42] of biological samples from pregnancy (e.g. blood samples) as a community resource. It was suggested that such a resource could attract interest and investment from the commercial sector to the field and would benefit from international collaboration and resource sharing. As noted above, such a resource should aim to include biological samples from different stages of pregnancy. It was pointed out that, to be able to control for additional factors (e.g. age), it would be important for samples to be linked with health data about the patient – although this could be done anonymously. Such a biobank could be integrated with the UK Biobank; the National Institute for Health and Care Research (NIHR), UK Research and Innovation (UKRI), and other charity funders would be well-placed to support this.

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[39] Lu J, *et al.* (2004). *Metabolism of thalidomide in liver microsomes of mice, rabbits, and humans.* J Pharmacol Exp Ther. **310(2)**, 571–7.
[40] European Medicines Agency (2018). *EMA guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation*. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-and-simulation_en.pdf. Note that the MHRA follows EMA guidance until or unless it introduces its own. In this case, MHRA assessors were strongly involved in drafting the guidance.
[41] https://www.hdrmidlands.org.uk/hdrproject/mum-predict
[42] A biobank is a large collection of biological or medical data and tissue samples, amassed for research purposes.

Health data records can be a useful resource for pregnancy research when linked to patient samples or in their own right. For example, health data from clinical practice could be leveraged to understand the impacts of medicines taken for other purposes during pregnancy on pregnancy-specific conditions, which could support drug repurposing. Participants highlighted existing data systems that could be built on to provide an additional resource for research in pregnancy, including the Secure Anonymised Information Linkage (SAIL) databank in Wales and the Clinical Practice Research Datalink (CPRD),[43,44] as well as research programmes organised by HDR-UK.

Data linkage[45] was noted to be of key importance to the usefulness of health data and patient samples in pregnancy research. Given the long-term health impacts of pregnancy and pregnancy-specific conditions, linkage to data about long-term health conditions, such as cardiovascular disease and diabetes, in both the pregnant woman and their child would also be useful for research. However, there is currently a lack of health data linked to patient samples and a lack of infrastructure in most of the UK for the linkage of the health data records of women and their children. Participants noted that this has implications for all areas of pregnancy research, for long-term follow-up of clinical trials as well as preclinical research. Participants suggested that more streamlined and ethically robust systems are needed to collect samples and associated health data and provide access to researchers. Some participants noted that linkage of health records of women and their children was supported by data infrastructure in Scotland and that some lessons learnt could be applied in the rest of the UK. Others noted that systems such as BadgerNet, which holds a single maternity care record on each woman that can be accessed by doctors and midwives wherever they are working, could be learnt from and built upon to be used as a research tool.

Next steps proposed by participants:

3.1. Undertaking a systematic review of emerging technological options for developing a better understanding of placental function to identify research opportunities.
3.2. Establishing a biobank or database of biological samples linked to relevant health data that are useful for pregnancy research, such as placental tissue and maternal blood samples. A mapping exercise of existing investments and initiatives would be useful to ensure best use of resources.
3.3. Reviewing the potential of new genetic technologies to create more accurate models of human pregnancy-specific conditions.
3.4. Reviewing the current status of PBPK modelling in pregnancy to identify knowledge gaps and research priorities.

[43] https://saildatabank.com/
[44] https://cprd.com/
[45] Data linkage involves joining information from different datasets to study links between different factors; for example, connecting the health records of mothers with markers of the health of babies.

3. The establishment of a more enabling environment for research in pregnancy, for example through the development of a stronger research base and a more supportive regulatory environment

Despite the extent of the unmet need, there is relatively little R&D activity in the UK focused on pregnancy-specific conditions and the development of new treatments. In part, this reflects a common perception that medicines development in this area is complex and high risk. Treatments are typically time-limited to the period of pregnancy, although some might have wider application outside pregnancy. Workshop participants therefore suggested that steps need to be taken to create an environment more conducive to R&D for the development of new treatments for pregnancy-specific conditions.

Research environment

A widely expressed view at the meeting was that the UK lags behind many other countries in its prioritisation of research in women's health, including pregnancy. It was felt that research in pregnancy has not been high on the agenda of policymakers and receives comparatively little research funding. According to one analysis, the UK invests £51 million a year in pregnancy research, which amounts to about 2.4% of non-commercial health research. For every £1 spent on pregnancy care in the NHS, less than 1p is spent on pregnancy research, a ratio far smaller than for other areas of health.[46]

The lack of prioritisation of research in pregnancy, as well as perceptions of limited funding opportunities, were thought to have led to a declining interest in and ability to work in this area. Participants expressed concern about the sustainability of the academic workforce involved in pregnancy-related research in the UK. It was noted that research in pregnancy, and women's health more generally, has not historically been prioritised. Since the workshop, the Department of Health and Social Care announced £50 million of NIHR funding to find ways to tackle maternity disparities, though it remains to be seen whether the development of treatments for pregnancy-specific conditions will be supported by this fund.[47]

Participants agreed that increased targeted funding for research in pregnancy and pregnancy-specific conditions was needed, with a long-term commitment to such funding. It was felt that very few funding calls had targeted research in pregnancy, so grant applications in this area have to compete with proposals alongside other areas of medicine. Additionally, participants noted funding and advisory committees typically do not have good representation of researchers with understanding of this field and its related challenges, meaning applications may be at a disadvantage. Some participants suggested that a Centre of Excellence in Pregnancy Research or women's health more broadly could be established as a flagship national initiative to signal a commitment to the field. Such a centre would benefit from cross-sector input from groups including government, the commercial sector and academia, and from long-term funding. However, they noted that a centralised hub alone, without regional presence, might make including under-represented groups more challenging.

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[46] https://www.rand.org/randeurope/research/projects/uk-pregnancy-research-needs.html
[47] GOV.UK (2024). *Health Secretary announces new women's health priorities for 2024.* https://www.gov.uk/government/news/health-secretary-announces-new-womens-health-priorities-for-2024. Note that this announcement was made after the workshop took place and so this funding was not discussed by workshop participants.

Regulatory environment

The importance of a supportive regulatory environment for pregnancy research was also stressed. The development of ICH guidelines on inclusion of pregnant women in clinical trials was welcomed as a key step for ensuring their more timely access to new therapies, as were other efforts to coordinate and align approaches across countries. Participants suggested that lessons could be learned from the COVID-19 pandemic, when regulators were praised for their flexibility and constructive engagement with the commercial sector in order to accelerate vaccine development and licensing. A suggested 'quick win' in the regulatory domain for preclinical pregnancy research could be the development of agreed physiologically based pharmacokinetic standards.

Participants suggested that it would be useful to engage with regulators to build confidence in the use of a more diverse range of tools and models to demonstrate the safety and efficacy of medicines, taking account of the limitations of traditional animal models such as rodents. Participants suggested that a cross-sectoral workshop or working group would be useful to build on previous activities such as the 2020 workshop organised by the MHRA on 'Predicting the safety of medicines in pregnancy'.[48] Such a workshop could examine the strengths and weaknesses of different animal models for the study of pregnancy-specific conditions, and establish in which contexts data could inform regulatory decision-making and what additional studies could be carried out to validate models. More broadly, some participants noted that a repository for researchers (from both academia and the commercial sector) of regulatory guidelines about research into medicines for pregnancy-specific conditions would be useful, including preclinical data needed prior to early phase clinical trials. The MHRA has a section providing 'Guidance for developers of new medicines' in their guidance on 'Use of medicines in pregnancy and breast-feeding', which can be updated as the new guidance is developed.[49]

Next steps proposed by participants:

3.1. Engaging with regulators to develop PBPK standards.
3.2. Exploring with regulators which data from which tools and animal models can be utilised to satisfy which regulatory requirements and to identify where additional validation studies would be required.
3.3. Raising awareness of regulator guidance for developers of new medicines in pregnancy and how this guidance applies to medicines for pregnancy-specific conditions.

4. Greater engagement with women to raise awareness of the importance of research into pregnancy and of opportunities to participate in this research

Participants agreed that more needs to be done to encourage pregnant women to participate in research about pregnancy. This includes women with pregnancy-specific conditions as well as women with healthy pregnancies, who have an important role to play in studies of healthy

[48] Clements J, *et al.* (2020). *Predicting the safety of medicines in pregnancy: A workshop report*. Reproductive Toxicology **93**, 199–210.
[49] MHRA (2021). *Use of medicines in pregnancy and breastfeeding.* https://www.gov.uk/guidance/use-of-medicines-in-pregnancy-and-breastfeeding#guidance-to-developers-of-new-medicines

pregnancy and as controls in disease-focused studies. Participation in such research can involve donating biological samples and/or giving permission to access health data. In addition to being participants in research studies, women can be involved in the wider research process, for example by advising on study design and the prioritisation of research questions. Although the workshop discussions were predominantly focused on preclinical research and experimental medicine, participants noted that the involvement and recruitment of women is also critically important for clinical trials of medicines.

Research participation

Participants highlighted that, in general, the possibility of participating in research is not often discussed with pregnant women. The difficulty of approaching women who have experienced the loss of a child or another adverse pregnancy outcome was also acknowledged. However, the representatives of patient groups emphasised that women who have experienced a pregnancy-specific condition often do want to take part in research given the opportunity, particularly because they may be at risk of the same condition in a subsequent pregnancy.

Various suggestions were made on how information about research and opportunities to participate in research studies could be conveyed to pregnant women. It was suggested that every contact a pregnant woman has with health services is a potential opportunity to raise awareness. Specific actions could include providing information in antenatal packs. Participation in research could also be raised during individual consultations with healthcare professionals. The benefits of contacting women before they become pregnant were also noted. One approach suggested was to include a link to a website with information on research in pregnancy, such as the NIHR/NHS Be Part of Research platform,[50] in patient information leaflets provided with pregnancy tests and/or antenatal information packs. Participants pointed out the importance of such information coming from a trusted source, such as NHS England.

Participants noted that the use of multiple different channels of communication would be beneficial to take account of differing preferences for receiving information. Social media or other communications outlets used by research charities or patient groups were felt to be possible ways to build awareness of research and research outcomes.

Participants also highlighted the importance of adopting an inclusive approach. Certain communities are less likely to access healthcare, will experience worse pregnancy outcomes,[51] and are less likely to participate in research. Typically, these disadvantages reflect socioeconomic and/or ethnicity-related inequalities.[52] The lack of inclusion of women in these communities in research studies could lead to the evidence generated being less applicable to them, potentially widening health inequalities. Reaching women in these communities will require an understanding of the barriers limiting their contact with health services as well as participation in research and sufficient resource to support outreach activities. As well as ensuring leaflets or other materials are accessible and available in languages other than English, researchers may also need to work with community-based organisations to build trust and establish better links with women from these communities. It was noted that such organisations often provide a gate-keeping function, filtering and translating the requests for their community to be involved in research to maintain the trust of their community and protect its interests.

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[50] https://bepartofresearch.nihr.ac.uk/results/search-results
[51] Thomson K, *et al.* (2021). *Socioeconomic inequalities and adverse pregnancy outcomes in the UK and Republic of Ireland: a systematic review and meta-analysis*. BMJ Open **11(3)**.
[52] Jardine J, *et al.* (2021). *Adverse pregnancy outcomes attributable to socioeconomic and ethnic inequalities in England: a national cohort study*. Lancet **398(10314)**, 1905–12.

Concerns about the safety of medicines, and the possibility of causing harm to the baby, were seen as the main barrier to participation in research and particularly clinical trials during pregnancy. Encouraging participation in minimally invasive research at an earlier stage in the medicine development pipeline (for example via donation of tissue or blood samples) was thought to be one way in which women could gain an initial experience of research. Giving permission for researchers to gain access to medical records would also be a comparatively risk-free way for women to participate in research. This familiarisation with research might encourage later participation in interventional trials.

Although risk tends to be a primary concern, it was suggested that risk communication around participation in research should be embedded within a more holistic risk–benefit framework that encompasses potential benefits as well as risks. Participants noted, for example, that people who take part in research more broadly generally have better outcomes. It was pointed out that levels of risk were heavily dependent on the stage of research, and that acceptability of risk is dependent on the past experience of women during pregnancy or family history. Consideration of these issues could support a more nuanced consideration of risk, and emphasises the need for consultation with women to accurately understand the opinions of different groups.

Given the long period of time it takes to develop, test and gain approval for new medicines, participants felt it important to be transparent that the women themselves might not benefit personally from participation in early-stage research studies, to avoid raising expectations. Nevertheless, there are several positive messages that can be conveyed about participation in research, including the potential gains for future women and the higher quality of care typically associated with research studies due to more intensive monitoring.

Involvement in research

As well as being participants in research studies, women with lived experience can also play an important wider role in shaping research and the research agenda, including through the prioritisation of research questions. Participants highlighted the importance of involving women with lived experience as early as possible in the development of a research study. This provides an opportunity for women with lived experience to have input into key aspects of study design, such as outcome measures, and how the study is conducted, so that it is convenient for, relevant to and acceptable to participants.

Participants suggested that women who had participated and/or been involved in research studies could be important advocates for research in general and research into pregnancy more specifically. Such role models could be featured in case studies produced by patient groups or discuss their experience at live events to help raise awareness of the opportunities and benefits of participation in research during pregnancy.

In summary, it was concluded that the aspiration was for participating in research to be 'normalised', or part of the culture of routine care, so that every pregnant woman has the expectation that they could participate in research if they wanted to.

Next steps proposed by participants:

4.1. Exploring initiatives to raise awareness amongst women about the opportunity to be involved in pregnancy-related research, including by linking to information about pregnancy research in the patient information leaflets of pregnancy tests.
4.2. Establish a group to develop a menu of opportunities and plans to promote the engagement of pregnant women in research.
4.3. Identify patient research advocates and tell their stories through case studies.

5. Education and training of healthcare professionals, including midwives, to promote research in pregnancy

Participants noted that the opportunity to participate in research as part of routine care depends on a trusting and informed relationship, both with health professionals and the health system in general. It was noted that women may not distinguish between researchers in academia and the healthcare system. During antenatal care, pregnant women typically have multiple contacts with the healthcare system. This provides an opportunity for healthcare professionals to introduce the idea of participating in research about pregnancy and to raise awareness of specific studies for which women might be eligible, for example by signposting the NIHR/NHS Be Part of Research platform.[53] Universally offering the opportunity to pregnant women to participate in research is already standard practice in some healthcare settings, such as clinics treating major complications in pregnancy at Manchester University NHS Foundation Trust; for example, the Velocity clinic provides multidisciplinary care to women with diabetes during pregnancy,[54] and the Manchester Antenatal Vascular Service supports women who have high risk of hypertension in pregnancy.[55] Participants felt that best practice from such examples should be shared and built upon elsewhere.

However, participants noted that healthcare professionals often do not encourage women's participation in research – and in some cases may even actively discourage it. This may be because of concerns about participation in research of any kind during pregnancy due to perceived risk, or lack of awareness specifically of preclinical research in pregnancy and the potential benefits. As illustrated by Caitlin Dean's experience described above, negative attitudes to research in pregnancy may reflect conflation with a more general concern among some healthcare professionals about medicine use during pregnancy.

There was felt to be a need for more training of healthcare professionals, either during their initial training or as part of continuing professional development, about the importance of research to understand pregnancy-specific conditions and ultimately to promote healthy pregnancies. Midwives in particular were seen as a critical group to work with, given their frequently close and trusting relationships with pregnant women. Expanding the numbers of research midwives could be one practical step forward.

Participants suggested that a consultation could be undertaken to gather information about current attitudes to preclinical research and experimental medicine during pregnancy, and what support relevant health professionals, including midwives and GPs, feel they need in order to communicate effectively with pregnant women about research opportunities. Dialogue with Royal Colleges could be one way in which to better embed awareness of research opportunities into healthcare professional activities. However, it was also acknowledged that time constraints and heavy workloads could make it difficult for healthcare professionals to effectively advocate for research, or to play a more active role in it. For this reason, it was suggested that healthcare professionals could signpost to platforms that collate and facilitate participation in research studies including those that are pregnancy-related, such as the NIHR/NHS Be Part of Research platform and NHS Research Scotland's initiative SHARE, rather than being expected to provide direct links to particular studies.

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[53] https://bepartofresearch.nihr.ac.uk/results/search-results
[54] https://www.tommys.org/research/research-centres/velocity-clinic
[55] https://www.tommys.org/research/research-centres/manchester-antenatal-vascular-service-mavis

Given the possible need for behaviour change among some healthcare professionals, the potential to adopt a behavioural science approach was highlighted. The COM-B model (capabilities, opportunities and motivation to change behaviour), for example, was suggested as one possible framework that could be adopted to support a systematically designed set of activities.

Next steps proposed by participants:

5.1. Undertaking a survey of relevant healthcare professionals (e.g. midwives and GPs) to explore attitudes, information needs, and their potential to be effective advocates for research in pregnancy.

5.2. Raising awareness amongst healthcare professionals about research in pregnancy to support them in constructively engaging with patients about opportunities to participate or be involved in other ways. Midwives would be a critical group to work with, given their frequently close and trusting relationships with pregnant women. Participants noted that Royal Colleges, including the Royal College of Midwives, the Royal College of Nursing and Royal College of General Practitioners, would be well placed to raise awareness, train healthcare practitioners, and help create the expectation of the offer of research participation as part of routine care during pregnancy.

5.3. Providing guidance to healthcare professionals about platforms that patients interested in participating in research studies can be signposted to, such as the NIHR/NHS Be Part of Research platform and NHS Research Scotland's initiative SHARE. Royal Colleges would be particularly well placed to do this.

6. Advocacy to secure greater prioritisation of research in pregnancy (and women's health more generally) by policymakers, funders and higher education institutions

Participants felt that research in pregnancy, and women's health more generally, was not seen as a high priority in the UK, and some commented that this could be seen as a gender equality issue. A common misconception is that pregnancy-specific conditions are rare,[56] although this is not the case: at least 1 in 20 pregnant women have gestational diabetes,[57] 1–8 in 100 have pre-eclampsia,[58] 1–4 in 100 have hyperemesis gravidarum,[59] 1 in 140 have intrahepatic cholestasis of pregnancy,[60] for example. It was felt that concerted efforts were required to raise awareness of unmet medical needs, as well as to promote greater investment in research and initiatives to encourage new medicines discovery and development for pregnancy-specific conditions.

One critical function of a research-in-pregnancy network or coalition, as discussed above, would be to advocate for greater prioritisation of this area. The importance of sharing evidence-based success stories was emphasised (such as the example in Annex 3), alongside information on unmet clinical needs.

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[56] A rare disease is defined as a condition that affects less than 1 in 2000 people.
[57] https://www.diabetes.org.uk/diabetes-the-basics/gestational-diabetes/causes
[58] https://cks.nice.org.uk/topics/hypertension-in-pregnancy/background-information/prevalence/
[59] https://cks.nice.org.uk/topics/nausea-vomiting-in-pregnancy/background-information/prevalence/
[60] https://britishlivertrust.org.uk/information-and-support/liver-conditions/intrahepatic-cholestasis-pregnancy

Participants suggested that taking a life course approach and emphasising the long-term consequences of pregnancy-specific conditions on the health of women and their babies could help to communicate the importance of developing treatments to decision-makers, and encourage greater investment in research in pregnancy from a public health standpoint. Several conditions, including gestational diabetes in mothers, increase the risk of other conditions and other metabolic disorders later in life. For example, pre-eclampsia doubles the risk of stroke, quadruples the risk of high blood pressure, and increases the risk of heart attack for the pregnant woman in later life,[61] and can also negatively affect the cardiovascular and neurological health of the baby.[62] Participants proposed increased collaboration with other areas of research and medical specialties to communicate the benefits of increased understanding of the physiology from a life-course perspective. Focusing on reducing the long-term consequences of pregnancy-specific conditions for such non-communicable diseases could open opportunities for partnerships with other medical research charities, leveraging greater resources for research, advocacy and public recognition.

Health economic analyses would be valuable to decisionmakers, such as analyses that demonstrate the potential for more effective prevention and for treatment of pregnancy-specific conditions to deliver cost savings. For example, the costs of fetal growth restriction described in Professor David's talk illustrate the immediate impact on NHS resources, but the condition also has long-term health, social and economic impacts that are currently unknown.

Participants suggested engaging policymakers in research fora, as well as multisector dialogue events including the commercial sector. Outputs from research studies could also be communicated in a more accessible and relevant way to policymakers and other non-specialists. The potential to learn from initiatives like the James Lind Alliance[63] was raised, and a prioritisation exercise to gather patient input into research priorities was suggested. However, some participants pointed out that similar exercises in the past have had limited impact.[64]

Other important stakeholders for advocacy groups to engage with include research ethics committees and regulators, in order to balance the need for effective evaluation of novel medicines for pregnancy-specific conditions and the challenges of the unmet need in terms of the consequences of untreated pregnancy-specific conditions. Dissemination of information to pregnant women and allaying misconceptions and concerns about research in pregnancy were also seen as critical objectives.

Next steps proposed by participants:

6.1. Collaboration between researchers (in both academia and the commercial sector), women with lived experience, regulators, funders, and patient advocacy groups to develop a national research agenda for pregnancy-related conditions, including a common set of research priorities.

6.2. Developing a coordinated advocacy strategy, covering health and economic arguments, to raise awareness among policymakers and promote additional investments in research for pregnancy-related conditions.

[61] https://www.bhf.org.uk/informationsupport/conditions/pre-eclampsia
[62] Lu HQ, Hu R (2019). *Lasting effects of intrauterine exposure to preeclampsia on offspring and the underlying mechanism.* AJP Rep **9(3)**, 275–91.
[63] The James Lind Alliance (JLA) is a non-profit making initiative bringing patients, carers and clinicians together in JLA Priority Setting Partnerships (PSPs). The JLA PSPs identify and prioritise unanswered questions or evidence uncertainties that they agree are the most important, so that health research funders are aware of the issues that matter most to the people who need to use the research in their everyday lives.
[64] https://www.jla.nihr.ac.uk/priority-setting-partnerships/hypertension-in-pregnancy/top-10-priorities.htm

Conclusion

Pregnancy-specific conditions can cause suffering, loss of life, and long-term health complications for mothers and babies, with associated economic impact, yet they remain a neglected area of health. At the end of the meeting, Dr Williams, the workshop Co-Chair, concluded that there was a large amount of passion and energy for developing treatments for women with pregnancy-specific conditions amongst experts working in the field, including workshop participants. Dr Williams encouraged participants to take advantage of collaborative opportunities and put the actions discussed in the meeting into practice. Professor Brocklehurst, the workshop Co-Chair, reflected that, beyond maternal health experts, many are unaware of the lack of medicines and investment in development of medicines for pregnancy-specific conditions, including healthcare professionals and members of the public. Dr Williams and Professor Brocklehurst therefore highlighted the importance of continuing the conversation on pregnancy research.

Medicine discovery and development for pregnancy-specific conditions is seen as challenging from both a technical and regulatory perspective, often discouraging commercial investment. Multiple steps could be taken to ensure a better-stocked therapeutic pipeline for pregnancy-specific conditions, including:

- Engaging with women from diverse backgrounds and involving them in research into pregnancy-specific conditions, to raise awareness of research and to help to identify key challenges and unmet needs.
- Undertaking advocacy for research into pregnancy-specific conditions and development of treatments, including communicating unmet needs and establishing research priorities to catalyse greater investment from funders.
- Establishing more interdisciplinary collaborations to advance understanding of the basic physiology of pregnancy and disease mechanisms of pregnancy-specific conditions.
- Using new mechanistic insights to develop improved disease models.
- De-risking investment in the development of medicines for pregnancy-specific conditions for the commercial sector; fostering closer collaboration between academia and the commercial sector on, for example, target identification and medicine discovery, could be one way of helping to achieve this.
- Engaging in further dialogue with regulators to identify and overcome key regulatory barriers to new medicine development for pregnancy-specific conditions.
- Making greater use of routinely collected health data and patient samples.
- Promoting education and communication with health professionals to encourage them to discuss participation in research with women.

Many of these priorities reflect the need for greater collaboration across scientific disciplines, sectors and stakeholder groups. An overarching theme was that progress is dependent on concerted and coordinated action, with key stakeholder groups – academics, clinicians, the commercial sector and patient groups – working together to engage with policymakers, funders, pregnant women and their families, relevant healthcare professionals and regulators to drive the field forward.

Annex 1: Agenda

<table>
<tr><th>Time</th><th colspan="3">Session</th></tr>
<tr><td>10.00 – 10.05</td><td colspan="3">Opening remarks from Co-Chairs
Professor Peter Brocklehurst FMedSci, Emeritus Professor of Women's Health, University of Birmingham; Director of Research and Development, Birmingham Clinical Trials Unit
Dr Pauline Williams CBE FMedSci, Independent Pharmaceutical Medicine Consultant, Former Senior Vice President and Head of Global Health R&D, GlaxoSmithKline</td></tr>
<tr><td></td><td colspan="3">Session 1: Developing treatments for pregnancy-specific conditions</td></tr>
<tr><td>10.05 – 10.15</td><td colspan="3">A journey in drug development for a pregnancy-specific condition
Professor Anna David, Director of the UCL Institute for Women's Health, Professor and Consultant in Obstetrics and Maternal Fetal Medicine
This talk was pre-recorded.</td></tr>
<tr><td>10:15 – 10:35</td><td colspan="3">Developing medicines to treat pregnancy-specific conditions
Dr Allyah Abbas-Hanif, Consultant in Pharmaceutical Medicine, Chair of the Faculty of Pharmaceutical Medicine's Paediatric and Women's Health Expert Group, Honorary Senior Clinical Lecturer, Imperial College London
This talk was pre-recorded.</td></tr>
<tr><td>10.35 – 11.00</td><td colspan="3">Perspective from a woman with lived experience
Dr Caitlin Dean, Spokesperson, Pregnancy Sickness Support</td></tr>
<tr><td>11.00 – 12.00</td><td colspan="3">Panel discussion with:
Dr Clea Harmer, Chief Executive, Stillbirth and neonatal death charity (Sands)
Marcus Green, Chief Executive, Action on Pre-eclampsia
Dr Janet Nooney, Expert Scientific Assessor (pharmacovigilance), MHRA
Dr Edith Roset Bahmanyar, Executive Director (Clinical Research & Development), Organon
Professor Catherine Williamson FMedSci, Professor of Women's Health, Imperial College London; Director of the Tommy's National Research Centre for Preterm Birth Research</td></tr>
<tr><td>12.00 – 12.15</td><td colspan="3">Break</td></tr>
<tr><td></td><td colspan="3">Session 2: Breakout groups</td></tr>
<tr><td>12.15 – 13.00</td><td colspan="3">Breakout Session 1: Exploration of barriers/enablers/priorities
Attendees were split into breakout groups and each given one of the three workshop aims (see below).</td></tr>
<tr><td></td><td>Research priorities for improving the understanding of pregnancy, including its physiology and pathophysiology (with a view to developing potential therapeutic options):
What key preclinical research gaps and opportunities exist? *
Why do these gaps exist?
What are the strengths and limitations of models used?</td><td>Tools and assays for exploring the efficacy, toxicology, pharmacokinetics, and pharmacodynamics of drugs for pregnancy-specific conditions:
What are the current and emerging technologies and methods that can be harnessed?
How can evidence generated using these models be</td><td>Enabling preclinical pregnancy research and experimental medicine, including via the health system:
How do women currently participate in research about pregnancy-specific conditions? (e.g. participating in or having their health data used in a study or contributing samples to a</td></tr>
</table>

	** This could include gaps in our understanding of the* mechanisms *of pregnancy and the* natural history *of pregnancy-specific conditions. Other gaps/opportunities may include the diagnostic infrastructure required for identifying patients at risk of pregnancy-specific conditions (e.g.* biomarker *identification and predictive tests).*	made acceptable to regulators and other key relevant groups? • Do we have the necessary infrastructure to enable use of emerging *models*?	study). Who are the key *stakeholders* involved in this? • What might facilitate or prevent pregnant women (including underrepresented groups) from participating or being involved in *preclinical* and *experimental medicine* research about pregnancy-specific conditions?
13.00 – 14.00	**Lunch**		
14.00 – 14.45	**Breakout Session 2: Overcoming barriers and identification of next steps** *In the same groups and relating to the same aim, participants discussed potential solutions to the barriers, how to develop enablers and meet priorities identified in the last session.*		
	Research priorities for improving the understanding of the *physiology* and *pathophysiology* of pregnancy. Participants might like to think about where and how research funding should be prioritised.	**Tools and *assays* for exploring the *efficacy, toxicology, pharmacokinetics,* and *pharmacodynamics* of *drugs* for pregnancy-specific conditions.** Participants might like to think about what evidence would be needed to allow research using emerging *models* of pregnancy to be accepted by researchers, regulators, and other *stakeholders*.	**Enabling preclinical pregnancy research and *experimental medicine*, including via the health system.** Participants might like to think about how patient *samples* can be gathered with sufficient relevant linked health data and how offering the option to be involved in pregnancy research could be made routine in the care of pregnant women.
14.45 – 14.55	**Break**		
	Plenary session – all delegates		
14.55 – 15.25	**Feedback & group discussion of proposed next steps:** Aim 1 – Research priorities for improving the understanding of the *physiology* and *pathophysiology* of pregnancy		
15.25 – 15.50	**Feedback & group discussion of proposed next steps:** Aim 2 – Tools and *assays* for exploring the *efficacy, toxicology, pharmacokinetics,* and *pharmacodynamics* of *drugs* for pregnancy-specific conditions		
15.50 – 15.55	**Short break**		
15.55 – 16.20	**Feedback & group discussion of proposed next steps:** Aim 3 – Enabling preclinical pregnancy research and *experimental medicine*, including via the health system		
16.20 – 16.30	**Closing remarks by the Co-Chairs**		
16.30	**Workshop close**		
16.30 - 17.00	**Networking**		

Annex 2: Participant list

Co-Chairs

- **Professor Peter Brocklehurst FMedSci**, Emeritus Professor of Women's Health, University of Birmingham; Director of Research and Development, Birmingham Clinical Trials Unit
- **Dr Pauline Williams CBE FMedSci**, Independent Pharmaceutical Medicine Consultant, Former Senior Vice President and Head of Global Health R&D, GlaxoSmithKline

Participants

- **Dr Khaled Abduljalil**, Senior Principal Scientist, Simcyp (Certara UK)
- **Professor Katherine Abel**, Professor of Psychological Medicine and Reproductive Psychiatry, University of Manchester
- **Dr Nada Abla Geiser**, Director, Drug Disposition and PBPK Modelling, Medicines for Malaria Venture
- **Kath Abrahams**, CEO, Tommy's
- **Dr Catherine Aiken**, Academic Clinical Lecturer, Honorary Consultant in Maternal and Fetal Medicine, University of Cambridge, Cambridge University Hospitals
- **Dr Anne Ammerdorffer**, Research Manager, Concept Foundation
- **Dr Edith Roset Bahmanyar**, Executive Director (Clinical Research and Development), Organon
- **Dr Elizabeth Bailey**, Associate Professor and Director of the Elizabeth Bryan Multiple Births Centre, Birmingham City University
- **Professor Philip Baker FMedSci**, Pro Vice-Chancellor, Research and Enterprise, University of Leicester
- **Jenny Chambers**, CEO and Founder, ICP Support
- **Lester Chinery**, Director of Programmes, Concept Foundation
- **Dr Jane Cleal**, Lecturer in Reproductive Cell Biology, University of Southampton
- **Dr Francesca Crowe**, Lecturer in Epidemiology and Health Informatics, University of Birmingham
- **Dr Jahnavi Daru**, National Institute for Health and Care Research (NIHR) Clinical Lecturer, Queen Mary University of London
- **Dr Caitlin Dean**, Spokesperson, Pregnancy Sickness Support
- **Professor Christian Delles**, Head of School (Cardiovascular & Metabolic Health), University of Glasgow
- **Elizabeth Duff**, Senior Policy Adviser, National Childbirth Trust (NCT)
- **Dr Kate Duhig**, NIHR Clinical Lecturer, The University of Manchester
- **Dr Christine Ekechi**, Consultant Obstetrician and Gynaecologist, Imperial College NHS Healthcare Trust
- **Dr Alice Fayter**, Programme Manager – Lifecourse & Ageing Research, Medical Research Council (MRC)
- **Dr Lucy Green**, Associate Professor in Developmental Physiology, University of Southampton
- **Marcus Green**, Chief Executive, Action on Pre-eclampsia
- **Sadia Haqnawaz**, Public Contributor, The Hilda's PPIE Group
- **Dr Clea Harmer**, Chief Executive, Stillbirth and Neonatal Death Charity (Sands)
- **Dr Kenneth Hodson**, Head of UK Teratology Information Service, UK Teratology Information Service (UKTIS)
- **Dr Holly Hope**, Research Associate, University of Manchester

- **Dr Jennifer Jardine**, Obstetrician and Researcher, London School of Hygiene and Tropical Medicine
- **Ian Jones**, Owner, Jinja Publishing Ltd
- **Farzana Kausir**, Public Contributor, The Hilda's PPIE Group
- **Professor Sara Kenyon**, Professor of Evidence Based Maternity Care, University of Birmingham
- **Dr Essam Kerwash**, Senior Clinical Pharmacology Assessor, Medicines and Healthcare products Regulatory Agency (MHRA)
- **Professor Asma Khalil**, Vice President for Academia and Strategy, Royal College of Obstetricians & Gynaecologists (RCOG)
- **Professor Marian Knight FMedSci**, Professor of Maternal and Child Population Health, University of Oxford
- **Dr Kathy Kordy**, Senior Director, Rare Disease Clinical Development – Immunology, Janssen
- **Dr Deborah Layton**, Principal Research Fellow, Drug Safety Research Unit
- **Dr Eliot Marston**, Deputy Director of Operations (Research), University of Birmingham
- **Jane Morrin O'Rourke**, Policy Manager, Health Research Authority
- **Dr Edward Mullins**, Clinical Senior Lecturer in Obstetrics, Imperial College London
- **Professor Jenny Myers**, Professor of Obstetrics and Maternal Medicine, The University of Manchester
- **Dr Janet Nooney**, Expert Scientific Assessor (pharmacovigilance), Medicines and Healthcare products Regulatory Agency (MHRA)
- **Dr Adeniyi Olagunju**, Tenure Track Fellow, University of Liverpool
- **Sonah Paton**, Co-Founder and Director, Black Mothers Matter
- **Dr Katherine Phillips**, Clinical Research Fellow, University of Birmingham
- **Professor Rebecca Reynolds**, Personal Chair of Metabolic Medicine, University of Edinburgh
- **Aimi Ritchie**, Medical Manager Immuno-Oncology, Pfizer
- **Dr Judy Shakespeare**, Chair, GPs Championing Perinatal Care (GPCPC)
- **Professor Gordon Smith FMedSci**, Professor of Obstetrics and Gynaecology, University of Cambridge
- **Professor Sarah Stock**, Professor in Maternal and Fetal Health, University of Edinburgh
- **Professor Alastair Sutcliffe**, Professor of General Paediatrics, University College London
- **Professor Michael Taggart**, Chair of Reproductive Sciences, Newcastle University
- **Zoe Taylor**, Public Contributor, Action on Pre-eclampsia
- **Professor Shakila Thangaratinam**, Dame Hilda Lloyd Chair of Maternal and Perinatal Health, University of Birmingham
- **Sarah Turner**, Operational Lead, Birmingham Health Partners
- **Dr Sara Webb**, Research Midwife, University of Birmingham and Head of Midwifery Information and Research Services, The Royal College of Midwives
- **Professor Catherine Williamson FMedSci**, Professor of Women's Health, Imperial College London; Director of the Tommy's National Research Centre for Preterm Birth Research

Staff and Secretariat

- **Rachel Bonnington**, Public Engagement Officer, The Academy of Medical Sciences
- **Hannah Chance**, Policy Officer, The Academy of Medical Sciences
- **Dr Claire Cope**, Head of Policy, The Academy of Medical Sciences
- **Dr Anna Hands**, FORUM Policy Manager, The Academy of Medical Sciences
- **Kate Little**, FORUM Policy Officer, The Academy of Medical Sciences
- **Charlie Vickers**, Public Engagement Officer, The Academy of Medical Sciences

Annex 3: Example of an integrated interdisciplinary approach to enhance understanding of pregnancy-specific conditions

Shortly after the workshop, a significant advance in understanding of hyperemesis gravidarum was reported, based on an international interdisciplinary collaboration led from the University of Cambridge. This work, which combined analyses of patient data and experimental studies, suggested that nausea in pregnancy is caused by the action of a protein produced by the placenta, known as GDF15, on the mother's brain.[65]

Furthermore, circulating levels of GDF15 before pregnancy appear to be associated with the severity of symptoms – low levels pre-pregnancy were associated with more severe symptoms. Increasing GDF levels before pregnancy might therefore be a way to reduce the risk of hyperemesis gravidarum.

The work illustrates a key message from the workshop: the potential for an integrated interdisciplinary approach, combining patient-related and experimental studies, to enhance understanding of pregnancy-specific conditions and to identify potential opportunities for intervention.

[65] Fejzo M, Rocha N, Cimino I, *et al*. (2024). *GDF15 linked to maternal risk of nausea and vomiting during pregnancy.* Nature **625(7996)**, 760–7.

Annex 4: Glossary of useful terms

This section provides definitions of research terms relevant to the workshop and pregnancy-specific conditions. For more extensive glossaries, please refer to one of the following sources:

- *https://www.nhs.uk/conditions/*
- *https://www.who.int/news-room/fact-sheets*
- *https://bestpractice.bmj.com/topics*
- *https://www.cedars-sinai.org/health-library.html*

Antenatal/prenatal
During or relating to pregnancy, often used to describe the medical care given to pregnant women before their babies are born.

Antibody-based medication
Antibody-based medications are types of targeted drug therapy that either enlist or block the body's natural immune system, by recognising and finding specific proteins. Their generic names all have the suffix 'mab', which stands for 'monoclonal antibody' – for example, trastuzumab (Herceptin) and rituximab (Mabthera). Some antibody-based medications help the immune system to attack and kill cancer cells; others can block signals that tell cancer cells to divide. Another example is certolizumab pegol, which treats autoimmune conditions, such as rheumatoid arthritis, in which the body produces too much of a protein called Tissue Necrosis Factor (TNF), resulting in inflammation, pain and joint damage. Anti-TNF drugs such as certolizumab block TNF and reduce this inflammation.

Assay (drug assay)
A detection tool or experiment designed to assess the presence, amount, or functional activity of a drug.

Biobank
A large collection of biological or medical data and tissue samples, amassed for research purposes.

Biomarker (biological marker)
A measurable indicator of a biological state or condition (e.g. a biological molecule found in bodily fluids that represents a particular process). Biomarkers are generally medical signs which can be used to detect an underlying condition or disease.

Cell
The basic building block of all living things, including plants and animals. Whether living on their own (e.g. bacteria, which are made up of a single cell) or as part of a multicellular organism, cells are usually too small to be seen without a light microscope.

Chromosome
A thread-like structure within cells that contains DNA (see below), tightly wound up and packaged so that it can be inherited from one cell to another.

Clinical trial
A type of clinical research designed to look at new ways to prevent, detect, or treat disease. Clinical trials rely on the participation of volunteers (participants) and follow a research plan created by the investigators running the study. Participants in a clinical trial may include people with a specific disease or condition and/or healthy volunteers. The goal is to determine whether a specific diagnostic, treatment, prevention, or behaviour approach is safe and effective.

Developmental and reproductive toxicology (DART) study
The goal of a DART study is to detect any effects of a drug within a complete reproductive cycle as relevant to humans – from initial conception of a fetus to the reproductive capacity in the next generation.

Data linkage
A method of bringing together information from different datasets about the same person or entity to create a new, richer dataset. This enables researchers to study links between different factors, for example by joining up the health records of mothers with markers of the health of babies.

Drug
Any natural or artificially made chemical that is used as a medicine to treat illness or injury. Drugs typically have a *physiological* effect when ingested or otherwise introduced into the body.

Drug candidate
A molecule being tested for *safety* and *efficacy* among other contenders, and usually showing favourable characteristics that justify further development.

Drug efficacy
A drug's capacity to produce a desired effect (curing disease or reducing symptoms) under ideal conditions – particularly whether the drug offers a health benefit over a *placebo* or other intervention.

Drug safety
Drugs can be harmful to *cells* (*toxicity*) and have unwanted side-effects, and these need to be identified and circumvented before use in humans.

Drug models
Drugs need to be tested for *safety* and *efficacy* in an external system before they are introduced into patients. They can be tested preclinically in predictive, cellular, and animal models before trials in humans:

- ***in silico*:** The drugs are tested using predictive **computer models** that estimate and predict whether they are safe based on existing knowledge (e.g. checking whether any chemical groups in the drugs have known interactions with any of the signals, hormones or pathways involved in the *physiology* of pregnancy).
- ***in vitro*:** The drugs are tested using a single layer of *cells* grown in the lab. These *cells* are not part of a larger system but are sensitive to *toxicity*, which allows *efficacy* and possible side-effects to be tested.
- ***in vivo*:** The drugs are tested for *safety*, *efficacy,* and dosage in **animal models** only if they are successful in predictive and cellular models. Individual *cells* and predictive models often cannot predict a drug's downstream effects, which might interrupt complex pathways and processes in the body. Testing in animals is usually more representative of how the

drug will perform within the complex environment of a living animal and provides the ability for longer-term follow up.

If drugs are safe and effective throughout preclinical trials, they can then be taken forward to clinical trials and tested in healthy human volunteers to assess *safety*.[66]

Embryo
An unborn offspring in the process of development, particularly a human offspring during the period from approximately the second to the eighth week after fertilisation (after which it is usually termed a *fetus*).

Experimental medicine
Studies or experiments conducted in human models to identify *mechanisms* of disease or *safety* and *efficacy* of new discoveries or treatments.

Fetus
An unborn offspring of a human or other animal in the stages of *prenatal* development that follow the *embryo* stage (in humans taken as beginning eight weeks after conception).

Gestation
The process or period of development inside the womb between conception and birth. Diseases or conditions that affect pregnant women may be referred to as gestational.

Mechanism (biology)
A system of interacting parts and processes that produce a function/effect.

Model system
An animal or experimental set-up designed for the study of specific biological processes, often to gain insight into how that process might happen in humans.

Natural history (disease)
The understanding of the progression of a disease process in an individual in the absence of treatment (i.e. the course a disease takes in an individual from its onset to its resolution).

Neonate
Newborn child, typically an infant less than four weeks old.

Obstetrics
The practice of caring for women after conception, throughout pregnancy, and during and after childbirth.

Omics
The scientific fields associated with measuring and processing biological molecules over large datasets. These fields include:

- **Genomics:** the study of all the genes (the basic units of inheritance) in an organism's DNA, as well as their functions and influences on the working of the body.
- **Proteomics:** the large-scale study and analysis of proteins.

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[66] Please note that the clinical trial stage is out of scope for this workshop.

- **Metabolomics:** the large-scale study of chemical processes involving small molecules, commonly known as 'metabolites', within organisms, *cells*, *tissues*, or bodily fluids.

Organ
A collection of *tissues* that structurally form a functional unit specialised to perform a particular function. Heart, kidneys, and lungs are examples of organs.

Organoid
A three-dimensional *tissue*, typically made up of stem *cells*, which models the key functional, structural, and biological functions of an *organ*.

Patient stratification
The separation of patients based on established criteria, which may include risk of disease, disease state, symptoms, gender, ethnicity, etc.

Pathophysiology
The biochemical processes and pathways that occur in the body in a disease state.

Pharmacokinetics
The study of how the body interacts with a drug for the entire duration of exposure, including the movement of the drug into, through, and out of the body.

Physiologically based pharmacokinetic modelling
Mathematical models that predict the movement of a substance into, through and out of the body.

Physiology
The biochemical processes and pathways that occur in the body in a healthy state.

Placebo
A dummy treatment that is designed to be harmless and to have no active properties. In a trial, a placebo looks, smells, and tastes like the treatment being tested, so trial participants do not know if they are taking the dummy treatment or the treatment itself. The effects of a placebo can be compared to a drug treatment to assess whether the latter has a significant effect.

Placenta
The organ that links the baby's blood supply to the mother's during pregnancy.

Postnatal/postpartum
Referring to the period of time immediately after a baby has been born; typically, the first 6–8 weeks after birth.

Preclinical
Preclinical development is the stage of research before clinical trials. Preclinical studies assess the safety and effectiveness of a product so it can then be tested in humans.

Sample (patient or clinical)
Matter obtained or derived from the human body, such as human tissue, blood, plasma, or urine samples. Sampling is usually performed to aid in the process of a medical diagnosis and/or

evaluation of an indication for treatment, further medical tests or other procedures including for *experimental medicine*.

Stakeholder
An individual or group that has an interest in any decision or activity of an organisation.

Therapeutic targets
A molecule, pathway or process that can be activated or inhibited by a type of therapy (e.g. a drug).

Tissue
A group of *cells* that have similar structure and that function together as a unit (e.g. brain/lung/muscle/fat tissue).

Toxicity
The degree to which a drug can poison the body and cause damage to an organism's *cells*, *tissues*, or *organs*.

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