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Healthy Mum, Healthy Baby, Healthy Future

The Case for UK Leadership in the Development of Safe, Effective and Accessible Medicines for Use in Pregnancy

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May 2022

Foreword

Baroness Manningham-Buller

When I was asked to become joint chair of the Commission that has produced this report, I am ashamed to say that I wasn't aware that there was an acute problem. Despite being at Wellcome for twelve years and Imperial College for six, I had no idea that research into conception and pregnancy was largely neglected, and that virtually no drugs had been developed and trialled for pregnant women in the many decades since thalidomide. This leaves women at the mercy both of general diseases, the diseases of pregnancy and drugs which are usually unlicensed. The evidence taken by the Commission in its inquiry convinces us that this urgently needs to change. We suggest how.

Baroness Manningham-Buller
LG, DCB, FMedSci

Professor Peter Brocklehurst

This policy commission report represents a clear and timely platform to improve the care we provide pregnant and breastfeeding women, by increasing the availability of safe, effective and accessible medicines for their use.

During the work of the Commission, we heard from pregnancy and baby charities, as well as experts from across a broad range of sectors. All of them, without exception, highlighted the profound lack of research activity in pregnancy – with 'research' covering the full spectrum of academic, clinical and industrial endeavour – and all expressed the need to do something to improve this terrible situation. Such consensus would not have been possible even 10 years ago, and it is a testament to all the individuals who have been championing this neglected area for so many years that we now have an opportunity to act.

And what is achievable, if all this report's recommendations were to be implemented in full? The stories of HIV and the Covid vaccine are two examples of what concerted and substantial investment in research can achieve. HIV infection, at least in affluent parts of the world, has become a manageable long-term condition with a wide range of medications available, a situation which was unimaginable 30 years ago. And several Covid vaccines were produced, tested, and then rolled-out within a year of the Covid pandemic starting. Imagine what could happen to conditions such as preterm birth or pre-eclampsia, conditions which have led to the deaths of millions of babies and many thousands of women within the UK and worldwide over the past decades, if we had a similar response and sense of urgency about developing new medicines to manage them.

We have an opportunity to make a real difference – let us not squander it.

Professor Peter Brocklehurst
MBChB, MSc, FRCOG, FFPHm, FMedSci
Professor of Women's Health
Director of Research and Development, Birmingham Clinical Trials Unit

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Note on terminology: While this report will refer to 'pregnancy', this term is used broadly to encompass pregnancy and breastfeeding. We use the terms 'woman' and 'mother' throughout the report, but the recommendations will also apply to people who do not identify as women and who are pregnant or have given birth. The term 'medicines' includes vaccines.

Note on geographical coverage: Whilst this report makes policy recommendations for the UK, there are no specific recommendations for policy in Northern Ireland, which is subject to EU regulatory oversight.

Disclaimer: This report is the product of a multi-stakeholder inquiry convened by the University of Birmingham and Birmingham Health Partners. The Commissioners have agreed its conclusions and recommendations. Individual points within the text do not necessarily represent the views of individual Commissioners. Nothing in this report can be taken as representing the views of the Commissioners' employers.

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Executive summary

The ongoing revolution in medicines and vaccines for longstanding and emerging health challenges has completely failed pregnant women.

Pregnant women and babies throughout the world continue to get sick and die from largely preventable or treatable causes. While the scale may be smaller, this is no less true in developed countries such as the UK. Despite this, the way in which medicines are developed currently risks preventing pregnant women from accessing the benefits of safe and effective medicines.

Recently, the exclusion of pregnant women from Covid vaccine trials has led to needless deaths amongst pregnant women and babies, tragically highlighting the issue. Failure is not simply a commercial issue – it is something which all parts of society must take accountability for and work together to solve. The Commission recognises that government expenditure is restricted as a consequence of world events but the cost of inaction is billions of pounds to the UK economy every year, causing untold physical and psychological effects.

The UK must take the opportunity to position itself at the global forefront of medicines development for use in pregnancy and breastfeeding, using the people, infrastructure and opportunities at its disposal.

This Policy Commission interviewed senior figures from pregnancy and baby charities, the NHS, universities, industry, and government, to help it set out a clear agenda for what needs to be done to improve the lives of millions of people, not just for women while they are pregnant, but for the health of future generations.

The interviews highlighted a number of reasons why medicines for pregnancy have not been developed and made a range of suggestions for how these could be overcome. This work will affect – and therefore must involve – a wide range of stakeholders at every stage. The Commission provides a blueprint for action and will provide ongoing support to implementing the recommendations set out in this report.

The UK Government's 'Vision for the Women's Health Strategy for England' identifies an urgent need to address severe health inequalities with respect to the access to safe and effective medicines for pregnant women, with maternal health identified as a key priority. The Commission hopes this report will be a helpful contribution, as government looks to develop and implement its strategy.

RECOMMENDATIONS

1. Deliver effective advocacy for medicines in pregnancy through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

2. Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy, unless there are specific safety concerns.

3. Prioritise updates for existing medicines with the potential to be used in pregnancy, with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

4. De-risk insurance processes for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

5. Incentivise industry to develop pregnancy-specific medicines, utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally-collaborative – position to drive drug development for pregnancy-specific conditions.

6. Establish a UK-wide national network of research centres encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. Improve use of routine clinical care maternity data to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. Appoint a UK Steering Committee aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

Introduction:
Why medicines in pregnancy matter

Most pregnant women will have a healthy pregnancy and give birth to healthy babies. An increasing number of women, however, will either have one or more health conditions before they become pregnant which require on-going treatment, or they may develop complications of pregnancy which require treatment. The care of these women is severely hampered by a lack of suitable medicines, that we definitively know to be safe and effective for use in pregnancy or during breastfeeding. As a consequence, women and babies worldwide continue to become sick and die during or immediately after pregnancy. Despite this, over the last 40 years, only two new medicines have been approved for use in pregnancy.

Each day globally
800 women die
7,000 newborns die
5,500 babies are stillborn

'Maternal health is a driver of human health and population health – without investment, the population will suffer. Population health drives economic stability and the health of a nation.'

Professor Neena Modi, Imperial College London and President of the British Medical Association

Around the world, every day, over 800 women and nearly 7,000 newborns die, while around 5,500 babies are stillborn. Almost all of these deaths are preventable. Pregnancy complications such as pre-eclampsia, prematurity, haemorrhage, infection and birth asphyxia account for the majority of these deaths.

While pregnancy in the UK is generally considered safe, women and babies are still dying needlessly as a direct result of preventable pregnancy complications: every year some 5,000 babies in the UK are either stillborn or die shortly after birth, and approximately 70 mothers die due to pregnancy-specific conditions. Others may have pre-existing and potentially life-threatening health conditions such as epilepsy, diabetes or depression, that are made more challenging to manage while pregnant.

Why is health during pregnancy particularly important?

Health during pregnancy has ramifications far beyond the outcomes of the pregnancy. Ill health during this period affects partners, wider family and society both in the short- and long-term. Childhood death and disability as a consequence of pregnancy complications have enormous, reverberating effects on people's lives and society as a whole. A stillbirth is not a 'one-off event', but can affect a family's mental wellbeing for life, with consequent social and economic costs. Preterm birth costs the economy £2.9 billion in a single year, according to a 2009 estimate of pre-term births in England and Wales. This includes the long-term costs of disabilities affecting 28% of the roughly 60,000 premature births in the UK each year.

What is more, pregnancy is a unique window during which the health and wellbeing of future generations is laid down. Our time in the womb and how we grow and develop before birth affects the risks of a range of diseases in adulthood, including diabetes and heart disease, as well as our general quality of health.

Improving population health can only be a gain in terms of individual and societal wellbeing; a healthy workforce underpins national wellbeing and prosperity, but that health begins during fetal life.

Medicines in pregnancy

Three out of four women take some form of medication during pregnancy. As society changes and more women become mothers at older ages, pregnancy may also become more medically complex. Pregnant women may have one or more underlying health conditions that require continuing treatment.

Women who require medication can have difficult choices to make when they become pregnant. Some medications are known to be unsafe to take during pregnancy, but suddenly stopping a medicine may result in even greater harm (see Epilepsy in pregnancy). This 'knowledge gap' as a result of inadequate scientific research and information is a huge problem, pushing the responsibility – and risk – of decision-making, in the absence of information, onto individual clinicians and women. Crucially, the root of medical inequality for pregnant women and their unborn children may lie within the wider context of gender bias in society. Many witnesses stressed that structural sexism may be a leading factor for the dearth of research and medicines in this area.

'We know that every day in the UK, 14 babies are either stillborn or die in the neonatal period… In some cases, medicines would not have saved the baby's life, but in many cases it might have done – and that's why it's such an important issue.'

Clea Harmer, Chair of the Pregnancy and Baby Charities Network

Pregnant women and their babies are denied the benefits of modern medicine enjoyed by the wider population, with potentially devastating results. The neglect of maternal medicines also hits those hardest who are already experiencing inequality in other areas of society. Black women are four times more likely to die from complications during pregnancy than white women; Asian women twice as likely. Older mothers, those from economically deprived groups, and mixed-ethnicity women are also more likely to die during or soon after pregnancy. In response, the Government has established a Maternity Disparities Taskforce to 'level-up' maternity care and tackle poor outcomes for women from ethnic minority communities and those living in deprived areas.

There is a real opportunity to address severe inequality with respect to access to safe and effective medicines in pregnancy, well-aligned with the current UK government focus on addressing health inequalities through the Women's Health Strategy.

The need to address this issue is beginning to be recognised around the world. The Concept Foundation, supported by the Bill & Melinda Gates Foundation have established the 'Accelerating Innovation for Mothers (AIM)' project. Designed to speed up maternal health research & development through global partnerships, the project aims to drive innovation of new medicines and technologies for pregnancy-specific conditions. Removing the stigma surrounding the inclusion of pregnant women in medicines research is central to the project.

Furthermore, the pharmaceutical industry have acknowledged their role in researching and developing new medicines in pregnancy. For example, the EU Innovative Medicines Initiative, ConcePTION, brings together over 60 partner organisations, including 16 pharmaceutical companies, to build a collaborative environment capable of providing evidence-based information on the safety of medications during pregnancy and create the first Europe-wide breast milk biobank for research purposes.

Epilepsy in pregnancy

Sudden unexpected death from epilepsy during pregnancy or in the following year has doubled in recent years in the UK, as shown by a 2020 MBRRACE report, which reviews all deaths of pregnant women and babies.

Women with epilepsy face a 'pregnancy lottery' with an impossible choice: do they take their epilepsy medication, several of which are known to increase the risk of major congenital malformations, and risk severe, long-term physical and neurodevelopmental harm to their babies? Or do they stop taking epilepsy medicines during their pregnancy and risk severe seizures, which also has consequences for their babies?

The use of epilepsy medicine in pregnancy has a difficult history. For decades, doctors prescribed sodium valproate during pregnancy, though since 1974 it has carried a safety warning that tests in animals had shown it could cause birth defects. Thousands of babies were subsequently born with physical and neurodevelopmental disabilities.

Patient-led advocacy, media and political attention eventually led to an almost complete ban of valproate in women of childbearing age, unless a pregnancy prevention plan is in place. However, a 2021 report by the Medicines and Healthcare Products Regulatory Agency (MHRA) Commission on Human Medicines revealed that a number of other anti-seizure medications taken in pregnancy could also cause harm to the unborn child.

'The clinical trials agenda has a major role to play in the Government's 'Levelling Up' programme.'

Rt Hon Sir Iain Duncan Smith MP, Rt Hon Theresa Villiers MP and George Freeman MP in Taskforce on Innovation, Growth and Regulatory Reform independent report, May 2021

The Commission

The 2021 report by the University of Birmingham and Birmingham Health Partners, 'Safe and Effective Medicines for Use in Pregnancy: A Call to Action' highlighted the absence of research and information on the safety of medicines in pregnancy. It also drew attention to the urgent health needs of this neglected group both nationally and internationally, and the potential for saving and improving millions of lives globally. The findings and recommendations presented here are the culmination of evidence gathered by a Policy Commission, set up in direct response to this earlier review.

Scope of the Commission

Convened by the University of Birmingham and Birmingham Health Partners, the Commission focused primarily on the UK, canvassing knowledge and opinions from key parties including patient groups, the pharmaceutical industry, scientists, clinicians, NHS leaders, regulators and insurers. It aimed to explore the scale of the problems that are preventing the evaluation and development of safe medicines for use in pregnancy and collected recommendations for how these could be overcome.

Aim

The Commission's overarching aim was to suggest solutions that, if enacted, could save the lives of women and babies, and improve the health of future generations. The UK is currently well placed to not only tackle critical inequalities at home, but to spearhead a global revolution for mothers and their babies, leveraging its National Health Service and independent regulatory environment.

Specific objectives:

1. To identify why there has been so little investment in evaluating the safety and effectiveness of medicines for pregnant women.
2. To identify specific barriers for patients, practitioners, policymakers, industry, and litigation experts in developing research in this field of medicine.
3. To provide solutions for overcoming the barriers identified, recognising the value all stakeholders can contribute and gain.
4. To drive tangible action positioning the UK as a leader in developing and testing safe, effective and accessible medicines for use in pregnancy.

Process of evidence gathering

Expert witnesses were asked to present evidence on the specific aims and objectives of the commission in relation to three main areas of unmet need:

- How we can improve the safety and effectiveness of existing medicines currently used in pregnancy.
- How new medicines developed for conditions in adults, which could be used in pregnant women, should be evaluated for use in pregnancy.
- How new medicine development for pregnancy-specific conditions for example, pre-term birth or pre-eclampsia could be facilitated.

See Appendices for a full list of Commissioners and Witnesses.

Creating a flourishing UK environment for change: opportunities, challenges and solutions

1. Clear and consistent messaging on medicines in pregnancy

The popular slogan 'Nothing about us without us' sums up one of the major planks of change: engaging with the public and patient voices – in this case, women and their families – in effective advocacy.

Historically, despite making up more than half of the population, women have been left out of key decisions on their health by a traditionally paternalistic system. The exclusion of all women, and then pregnant women, from clinical trials after the thalidomide tragedy stems from the medical maxim 'first do no harm'. Ironically, this move to protect pregnant women may have done the opposite, denying women and babies numerous advances in modern medicines.

Awareness is key, and lack of it may be one of the reasons why vociferous pressure has not come from pregnancy and baby charities on the issue of neglect in medicines for pregnancy.

Those women directly affected in pregnancy may become aware of the paucity of information and research only when they conceive, for example, because they have a condition like epilepsy, or because they develop a complication such as pre-eclampsia.

Women actively seek information on research in pregnancy, and evidence suggests they want to be involved in research, particularly if there is already a risk to their unborn baby's health. Although pregnancy may be a short window of time, its effects are lifelong and generational, as witnesses pointed out.

A number of charities including Action on Pre-Eclampsia, the Epilepsy Society and the National Childbirth Trust handle enquiries from concerned pregnant women and their families via dedicated helplines. But these charities are small compared with patient charities in some other areas, such as Cancer Research UK or the British Heart Foundation, which show vocal and effective advocacy across a single unifying health context.

The evidence heard by the Commission suggests a strong imperative for one unified voice from pregnancy and baby charities on the issue of the evaluation and development of medicines for use in pregnancy. Encouraging smaller parent and baby charities to come together might provide more effective and powerful lobbying. There may also be lessons to learn on unified advocacy from other areas.

It is possible that through increased awareness of the issues with the use of medicines in pregnancy, a woman's assumption that a medicine used in pregnancy has been thoroughly tested may be challenged. This could result in them deciding not to take the medicine at all, resulting in even greater harm to them and their baby. An important part of raising awareness will therefore be to ensure that women know that in order to have a healthy baby, they need to be healthy in pregnancy. This may mean taking medicines which may not have been thoroughly tested but where the likely benefits outweigh the possible harms.

> ***'A healthy baby needs a healthy mother to have a healthy start. It is not fair or right and it is very short sighted to exclude pregnant and breastfeeding women from clinical trials.'***
>
> **Professor Catherine Nelson-Piercy, Consultant Obstetric Physician at Guy's and St Thomas' NHS Foundation Trust**

Risk is a hard concept to convey, but, as one witness explained to the Commission, 'difficult and complex' are not reasons 'to look away'.

In addition to a lack of awareness that there is a problem with our existing knowledge about the effectiveness and safety of many medicines which are widely used in pregnancy, we heard repeatedly that the information we do have is poorly presented to clinicians and women. Currently, there are many different sources of information on medicines in pregnancy – and these may give different messages, may be unverified or be superseded by more recent research evidence. This makes it difficult for women to make an informed decision, and for healthcare professionals to give up-to-date, consistent information. Unified, coherent, and trusted sources of information about medicines currently used in pregnancy for both pregnant women and healthcare professionals are essential, but currently lacking.

Reliance on and influence of social media for medical information, and increasing polarisation of views may need to be taken into account in advocacy and any future communications strategy. A witness from the pregnancy and baby charity sector highlighted personal threats to their junior staff during promotions of their flu vaccine campaign to pregnant women during the Covid pandemic.

The growing reluctance among younger pregnant women to take any kind of medicines was also noted by clinicians. Setting up an overarching body to improve the way women and healthcare professionals receive information would help, as well as better training for midwives, doctors and pharmacists on medicines in pregnancy. The MHRA recently set up the Safer Medicines in Pregnancy and Breastfeeding Consortium to bring stakeholders together to improve the health information that women receive.

Together, evidence heard by the Commission points to fragmented, incoherent advocacy and information on medicines in pregnancy within the UK, causing severe detriment both to individual women and the wider case for change.

'Unexpectedly, pregnant people are remarkably willing to participate in drug trials…the willingness to consume something resulting in a better outcome for babies is something people embrace very, very positively.'

Jane Brewin, Chief Executive of Tommy's Charity

Recommendation 1

Deliver effective advocacy for medicines in pregnancy through a coalition of pregnancy and baby charities, working together with the public, researchers from academia and industry as well as Government to create a shared vision for safe medicines evaluation and development in pregnancy. This will allow for clear and consistent messages to the public and clinicians.

Learning from the End Violence Against Women (EVAW) Coalition

Established in 2005, EVAW brought together a coalition of 124 specialist women's charities (UK based and international), academics, activists and NGOs to deliver a unified voice to demand action from the UK government and international bodies to tackle violence against women and girls (VAWG).

In response to EVAW's effective advocacy and lobbying, the public profile of VAWG grew larger and louder and the government stepped up its response by announcing its Ending Violence Against Women and Girls Strategy (2016-2020) and the commitment of £80 million in funding to support frontline work such as refuges, national helplines and rape crises centres. Cross-society collaboration was integral to this strategy and required a cross-government approach which included the Home Office, the Department for Education, Government Equalities Office and the Foreign, Commonwealth and Development Office. Dedicated teams and resources were set up across government departments to drive the strategy.

In 2021, the government announced its continued commitment to tackling VAWG through a refreshed strategy, passed the Domestic Abuse Act and introduced mandatory training and statutory guidance for frontline professionals. Through EVAW's coherent voice, the "visibility and urgency" of VAWG in the public mind led to policymakers making prevention a key strategy. The UN Women's Prevention Framework, the UK's Violence Against Women and Girls Strategy and London's 'VAWG' strategy show that prevention policy is now a priority at the local, domestic and global level.

Uniting charities, health providers, academics, and policymakers, EVAW's strategy provided a unified approach, resulting in cross-sector collaboration, a clear VAWG strategy, dedicated resources across government, and legislative change. The same commitment must be applied to advocate for women and their unborn babies put at risk of death and disability by the lack of medicines in pregnancy.

2. Inclusion of pregnant women in clinical trials

Developing, testing and bringing to market medicines for pregnancy is seen as inherently risky by regulators, industry, academia and the insurers that underwrite clinical trials, due to the lack of fundamental biology, safety knowledge and advice. This is perpetuated by the legacy of thalidomide, and other medicines in the past that were shown to have adverse effects in unborn children. In the case of the medicine diethylstilbestrol (DES), which was given to women at risk of early miscarriage, the effects were generational. It was linked in the 1960s to vaginal and cervical cancers in daughters exposed to DES while they were in the womb, and subsequently to pubertal, menstrual and pregnancy complications in their children.

Thalidomide was never tested in humans – tests in chickens did not reveal any birth defect problems. Today's environment for testing new medicines is very different from that in the 1950/60s.

Industry and regulators are generally considered to be conservative in their approach. And while caution may be considered a virtue in this area, over-caution has led to unintended and grave consequences as it means that pregnant women are left without safe, effective and accessible medicines.

While lessons learned from thalidomide prompted the birth of modern pharmacovigilance (monitoring for safety) and have undoubtedly prevented further tragedies, there is a concern that by being too precautionary, society may be unburdening its responsibility to assess risk unfairly onto individual women and healthcare professionals. The Commission heard the same message many times from different sectors: that deciding on a medicine's risk in pregnancy is too often left to the individual woman to bear.

Concerns about regulatory and ethical approval may hinder research. However, the idea that clinical trials in pregnancy won't receive approval is a myth, said one witness from the MHRA, who stressed that approvals are made on a case-by-case basis.

The consequences of a lack of clear expectations around inclusion, as well as confused messaging on medicines in pregnancy can be disastrous. The rollout of vaccination against Covid in pregnant women is a case-in-point (see The Calamitous Case of Covid Messaging), where exclusion of pregnant women from clinical trials coupled with a lack of cohesive public messaging has had dire consequences.

> ***'After thalidomide and DES, the approach to risk management wasn't proportionate. A lot of […] that is based on the idea that thalidomide had been tested in pregnancy – but it had not. They were managing the wrong risk. But like a bump in the carpet if you push it [the risk] down somewhere, it comes up elsewhere.'***
>
> **Professor Richard Ashcroft, Deputy Dean and Professor of Bioethics, City Law School**

The Commission heard a strong case for introducing licensing requirements for all new medicines that would make testing for use in pregnancy compulsory in most cases. This type of 'Maternal Investigation Plan' (MIP) would draw on the experiences of the 'Paediatric Investigation Plan' (PIP) brought in by the European Union in 2007.

Under this regulation, companies applying for licences for new medicines must present a plan to study the medicine in children (unless inappropriate for this age group). In return, those with a successful plan receive a six-month patent extension. This scheme greatly improved the product pipeline for children's medicines, creating some 260 new medicines or indications for children since its launch. The proportion of clinical trials in children rose by over 50% with the new PIP regulations.

A similar MIP approach should be seriously considered. The Commission noted, however, that some drawbacks to PIPs were also highlighted. Some experts questioned how beneficial PIPs have been in reality, sometimes making adult drugs 'go through the mill' when they had no appropriate use in children. In other cases, PIPs had had unanticipated consequences leading to medicines being withdrawn. One witness said: 'There's nothing worse than hearing from a paediatrician that a key cancer medicine has gone.' One approach might be to pilot MIPs for a short period to gauge their effectiveness in light of this information.

In addition, a MIP structure should challenge the practice that women are automatically removed from trials if they become pregnant during the trial. A review to assess the safety of ongoing participation should be undertaken rather than automatic removal.

Introducing some licencing requirements for new medicines to be considered for use in pregnancy would require significant cross-sector working between regulators, clinicians, researchers, industry and pregnant women themselves – but such an environment could open up a new market for novel therapies.

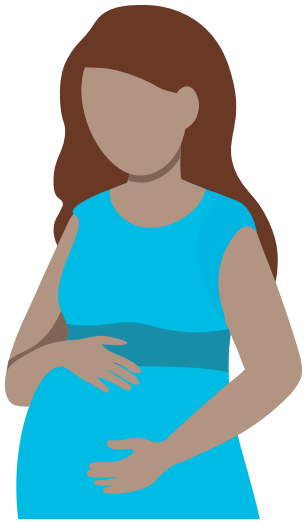
Together, the Commission heard a clear need for regulators, as well as other relevant health research bodies, to make explicit the need for pregnant women to be included in trials. In this context, regulators should be viewed very much as 'enablers' rather than 'barriers', and as proactive partners in the innovation process.

'Excluding pregnant women from the Covid vaccine trials has resulted in pregnant women dying needlessly.'

Professor Peter Brocklehurst, University of Birmingham, on behalf of the Commission

'You cannot justify developing a treatment in a way that excludes 50% of the people who might benefit from it. That is unethical. It is unjust.'

Professor Richard Ashcroft, Deputy Dean and Professor of Bioethics, City Law School



Recommendation 2

Pregnant women should be offered the opportunity to take part in all clinical trials of medicines that could be used in pregnancy, unless there are specific safety concerns.

The Calamitous Case of Covid Messaging

While the incredibly rapid development and rollout of vaccines for the Covid pandemic has demonstrated just what can be achieved when governments, funders, regulators, industry and universities pull together in a crisis, one group of the public has been hugely underserved. Changing and confused communications on vaccination in pregnant women has had tragic and fatal consequences.

Pregnant women were excluded from all of the early Covid vaccine trials, so that when vaccination was initially rolled out, pregnant women were not called forward because there was uncertainty about whether the vaccines were effective in pregnancy and whether they were safe.

The public messaging changed once real-world data became available, and pregnant women were advised to get vaccinated (from December 2020). Unfortunately, by then, the message had become confused, with many pregnant women and health professionals believing the vaccine was unsafe in pregnancy.

As a result, Covid wards and intensive care units filled up with unvaccinated pregnant women. A Health England report in October 2021 showed that one in five of the most critically ill Covid patients in hospital were unvaccinated pregnant women.

The RECOVERY trial was set up to identify treatments for all ill patients with Covid but did not initially consider including pregnant women until a month after it was set up in 2020, after strong lobbying efforts. Nevertheless, many health professionals remained reluctant to give the treatments that this trial has shown to be effective to pregnant women, due to a fear of treatment in pregnancy among practitioners.

1 in 5

of the most critically ill Covid patients in hospital were unvaccinated pregnant women.

3. Up-to-date pregnancy information for existing medicines

The commission heard that existing medicines information – the known, current evidence about individual medicines in relation to pregnancy – may in some instances not be fully up to date with the latest evidence and is usually extremely cautious. By updating information available for identified, appropriate medicines, at least more accurate safety information would be available to patients and healthcare practitioners. Significant progress on this front has been made recently in the US, which the MHRA has been closely monitoring.

We can also make better use of the data we already have – or could potentially have. For example, pre-licensing data on medicines could be sought from drug developers. We often have decades of post-marketing data on many medicines that are used by pregnant women or given "off-label" by doctors – however the medicine's Summary of Product Characteristics (the reference information for health care professionals on how to use the medicines safely and effectively) may not reflect all currently available evidence, particularly for older "off-patent" medicines. Healthcare professionals and pharmacists in the UK commonly rely on the British National Formulary (BNF) as a reference guide to prescribing. But their information may be outdated because it is based on the Summary of Product Characteristics – and this, the Commission was told is 'very cautionary'.

Work between global regulators, together with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), could provide a significant and timely step-change in available information, enabling more effective decision-making by both clinical professionals and the public.

> ***'We need one body - the BNF [the British National Formulary], the MHRA, the ABPI [Association of the British Pharmaceutical Industry] are all pulling in different directions.'***
>
> **Professor Catherine Nelson-Piercy, Consultant Obstetric Physician at Guy's and St Thomas' NHS Foundation Trust**

Recommendation 3

Prioritise updates for existing medicines with the potential to be used in pregnancy, with regulators and industry working towards pregnancy-specific information on safety, dosing and effectiveness. Resources should be put in place to maintain this activity, particularly for generic medicines.

4. Reducing R&D risks in pregnancy

The fear of litigation is a major concern for those developing medicines. In the UK, the compensation settlement for a baby damaged while in utero has been as high as £37 million. This could rise to a staggering US$110 in the US, where juries are involved in awarding compensation.

A hugely important element in de-risking clinical research, especially given the concerns over litigation, is the area of insurance. Industry and academic researchers currently struggle to find insurance for clinical trials involving pregnant participants, and likewise insurers grapple to assess the risks of these studies given so few are conducted and so few have resulted in any litigation (see Overcoming the insurance 'chicken-and-egg' situation).

Insurers rely heavily on the existing experience of clinical trials in making their assessments of risk, and with so few trials conducted in pregnancy, this is lacking. A combination of these factors means their premiums may be disproportionate to the compensation limits they can offer.

However, with more data and a better assessment of risks, premium costs may be reduced and insuring trials in pregnancy could be seen as less of a gamble. There is precedence in this scenario. Clinical trials of children's medicines were once seen as 'incredibly risky', but since the advent of Paediatric Investigation Plans (PIPs) and other initiatives such as the Medicines for Children Research Network, the number of clinical trials of medicines in children has increased substantially, meaning that insurers no longer view them with such concern.

While there is willingness from insurers to address these issues, they cannot do so without input from government and possibly regulators and the research community. Co-insurance with government, and collaboration between insurers, was suggested as a solution. There is an example for this working effectively as in the case of insurance against terrorism in the UK. Here, the UK government agrees to pick up the excess on a claim by the commercial sector if it is too large to be covered by the insurer under a scheme called 'Pool Re'.

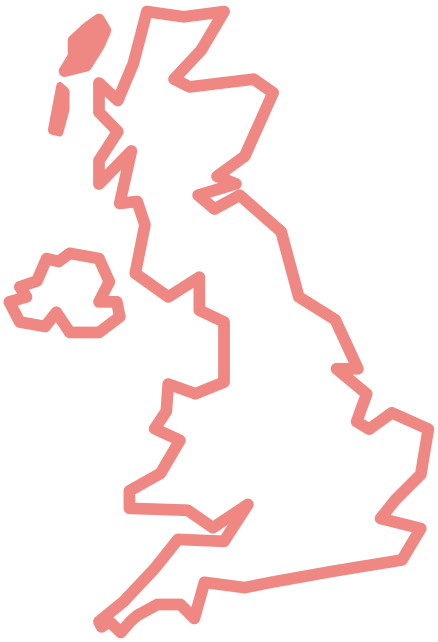
A similar agreement was made by the government and Lloyds of London regarding business interruption insurance during the Covid pandemic. A system akin to Pool Re would be a workable solution for insuring clinical trials of medicines which include pregnant women.

Insurers noted that this would probably only be needed for the short-term as an increase in clinical trials activity would provide more data to be able to confidently assess risk. Short-term investment by the government might also lead to high returns, enabling the UK to become a global hub for pregnancy research, backed by the insurance industry. The UK is already well placed to tackle this, as Lloyds has a global network with licences already in place across many territories. The human and real financial cost, through litigation and long-term costs associated with issues such as pre-term birth, should also factor into decisions on investment.

Together, the Commission was convinced of the significant opportunities to mitigate perceived risk and accelerate innovation through effective collaboration between government, insurers and researchers. And the good news is that with an initial boost, this area could grow becoming self-sustaining within a few years. The Commission recognises that initial investment will be costly but strongly urges the Government to factor in the cost of doing nothing.

'Far more people die from failure in this area than from terrorism. If we can arrange insurance for terrorism we should be able to produce a similar scheme for pregnant women.'

Baroness Manningham-Buller, House of Lords, Co-President of Chatham House, Co-Chair of the Commission



In the UK

the compensation settlement for a baby damaged while in utero has been as high as

£37 million

Overcoming the insurance 'chicken-and-egg' situation
Insurance is vital in order for clinical trials to be run. To underwrite or insure clinical trials – or indeed anything – insurers and their actuaries need real-world data to calculate risk, particularly how many claims are made by clinical trial participants, and what is the value of the settlements. But how do you accurately calculate risk if there is no data, or very little?

There are extremely few pregnancy intervention studies. Even at the University of Oxford – where 3,311 clinical studies are currently being led – only 2% of those were able to involve pregnancy (mainly surveys or observational in nature).

The few studies also means that pregnancy is not seen as a profitable area for insurers. Rather, the potential costs of claims are enormous because the standard form of clinical trials insurance in the UK is on a 'no-fault basis'. In other words, the burden of proof is not on the trial participant.

According to insurers, it is difficult to assign responsibility for potential birth defect effects, given the relatively high frequency of birth defects in the general population, which is approximately 1 in every 47 births in the UK.

'Pregnancy forms that potential perfect storm where you have high claim severity, and you have this latency between the intervention and the potential congenital abnormality arising, which means that you may have large numbers of participants exposed before you see the side effects.'

Ben Ward, Insurance Underwriter, Newline group

Recommendation 4

De-risk insurance processes for early and late phase clinical trials of new and existing medicines for use in pregnancy, using lessons and successes from other challenges.

5. Stimulating the market

Bringing any new medicine to market is a long process requiring significant investment, with only around one in ten medicines entering clinical trials ever making it to market. Under the classic pharmaceutical industry business model, areas such as medicines for use in pregnancy are often unattractive because of high perceived risks and excessive costs, complex studies and onerous regulatory hurdles. Perceived risks and low financial rewards for treatments during a relatively short-term physiological change – i.e. nine months – can make investment in pregnancy unattractive. However, some 210 million women become pregnant each year, which is a significant population with unmet need.

For established medicines used for non-pregnancy conditions, there are no incentives for testing in, or repurposing for pregnancy, with concerns about new risks arising from their use in pregnancy acting as a deterrent. Additionally, concerns about stigma and reputational risk are high in case complications in a clinical trial in pregnancy arise.

Alongside interventions which mitigate risk, there is a need to explore and implement economic incentives, such as the extension of a medicine's licensing patent. We could encourage approaches such as 'parallel trials', whereby clinical trials are run at the same time including both the general population and pregnant women, avoiding delay to a medicine's availability to the general population without depriving women of potential benefits in specific studies related to pregnancy. Many lessons can be learned from children's medicines and development of therapeutics for rare, or 'orphan', diseases.

Together, the Commission heard compelling evidence that mitigation of risk also required effective tools and approaches to stimulate innovation in this field, leveraging good practice whilst ensuring effectiveness in this specific context.

The Commission heard evidence of the difficulties in designing and conducting trials of medicines for pregnancy specific conditions due to the existence of different medical definitions of conditions, diverse standards of care for control groups, and different outcomes for studies. As medicines trials are often international, this is true across countries and as well as within countries such as the UK.

The lack of uniformity presents many practical difficulties for industry and academic researchers conducting trials in pregnancy. Where study participants may need to be recruited in the labour ward, obtaining fully informed consent in stressful situations may be challenging. The need for long-term follow-up of mothers and infants can also present difficulties.

Better collaboration between international regulators is also needed for the harmonisation of guidelines and to align the regulatory requirements, especially as trials in pregnancy may involve multiple sites across many countries to recruit a sufficiently large patient cohort to make trials results meaningful.

The Commission was convinced of the urgent need for work to standardise practice, processes and pathways for clinical trials and regulatory approvals in pregnancy at both a national and global level, and that setting standards for pregnancy medicine evaluation represented a real opportunity for UK leadership.

There does seem to be a growing desire and movement to tackle some of these issues among regulators including the UK's MHRA, EMA and the US Food and Drugs Administration.

Newfound regulatory independence promises the possibility of streamlined medicines development. In particular, the MHRA has developed a new fast-track process called the Innovative Licensing and Access Pathway (ILAP), and it believes that medicines for pregnancy, for example for pre-eclampsia, would be a good fit for this.

Industry could be further incentivised by early and efficient access to study participants; through the creation of new market opportunities which are "de-risked" through shared approaches to affordability; and working with the Commercial Medicines Unit within the NHS to agree joint-working with regulators, the NHS and NICE to incentivise the development of medicines and therapies in this area. The UK has the potential to collaborate with regulators and health bodies across the world on appropriate incentives, opening up new markets and opportunities for industry.

Recommendation 5

Incentivise industry to develop pregnancy-specific medicines, utilising cross-stakeholder working to ensure that the UK is in a globally-competitive – and globally collaborative – position to drive drug development for pregnancy-specific conditions.

6. Increasing investment in pregnancy research

Reproduction and childbirth is a 'Cinderella' area of research. It receives neither the funding, attention, nor status that other areas of science and health research garner. Though this area directly affects up to 51% of the population – in truth the entire population, since we are all a product of reproduction – only 2.1% of health research funding in the UK is spent on reproductive health and childbirth.

The UK spends about £51 million a year on pregnancy research, a small fraction of which is relevant to medicines use in pregnancy. For every £1 spent on pregnancy care in the NHS, only 1p is spent on research. For comparison, pregnancy-related litigation costs to the NHS in 2018-19 were £2.5 billion, making up approximately 49% of the total cost of clinical negligence claims.

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making up approximately 49% of the total cost of clinical negligence claims.

This paucity of investment – and subsequent paucity of pregnancy R&D – has serious knock-on effects. One witness noted that the UK remains 'at a 1990s level for progress in this field', where other areas of health science have flourished. This deficit runs through every stage from basic biology to pre-clinical medicines screening, and translation into novel therapies and other interventions which could save lives and relieve suffering for many mothers and babies.

Despite remarkable scientific advances in our understanding of human health and disease in other areas, we know little in comparison about basic human reproductive biology – the early embryo; how medicines affect the workings of the placenta; how medicines cross the placenta from mother to child; the handling of medicines by the fetus; and much of the basic physiology of pregnancy is still poorly understood. Improved understanding of discovery science in reproductive health and embryology is vital. Many of the issues in pregnancy are laid down at the earliest stages – in the first 12 weeks of gestation - so knowing the science of this early stage may be particularly crucial.

Understanding these basics better would help at an earlier stage in the process of designing and developing medicines for use in pregnancy. For example, if researchers could show that a new medicine does not cross the placenta at all, this would provide some reassurance for testing that specific drug in clinical trials with pregnant women.

Better pre-clinical tests would lead to a more secure and safe knowledge base before medicines go into clinical trials with pregnant women. This would mean potentially, that medicines likely to be harmful in pregnancy, would be screened out early. Good *in vitro, in vivo* and *in silico* models are needed to screen drug candidates and test the potential effects of medicines given in pregnancy, before the human clinical trial stage.

However, our lack of basic research knowledge and the unique nature of human pregnancy have been barriers.

There are no good animal models to test medicine candidates in pregnancy. Those commonly used have very different placental systems from humans, and do not naturally develop the pregnancy complication pre-eclampsia, for example.

Recent advances bring some hope to the field. A human placental stem cell line was successfully developed by Japanese researchers in 2018. And technological improvements in areas such as 'virtual' clinical studies, better computer modelling, microfluidics and organoids (bioengineered mini organs in the lab) means that we may see effective 'placenta-on-a-chip' models in the next three to five years. The UK could pioneer these technologies, and in turn accelerate pregnancy medicines research faster - provided research investment was prioritised.

The Commission also heard from different sectors that the low status and funding of reproductive science creates difficulties in attracting and retaining researchers. Too often, young scientists are lost to higher-profile and better-resourced areas such as cancer. This is also a challenge on the clinical side of research and care – there are fewer than 10 obstetric physicians in the entire UK, mostly based in London and Oxford.

Together, the Commission was convinced of the need for a clear national strategy related to pregnancy research, to address funding issues across the field: from discovery and translational science to clinical trials and evaluations; and to make the sector more attractive to recruit and retain talented researchers. There was also a compelling rationale to develop better and more efficient pre-clinical screening tools and reproductive toxicology models. Providing clear focal points of public and private investment as 'hubs' for a coherent UK community, well-linked with wider global funders and innovators, will be crucial to accelerating progress.

'We basically do not understand enough about the physiology of normal pregnancy and certainly about pregnancy complications, in order to know what we should be targeting.'

Professor Graham Burton, University of Cambridge

Recommendation 6

Establish a UK-wide national network of research centres encouraging major public and private investment and collaboration in pregnancy research expertise and infrastructure. This will ensure sustainable drug development from discovery science through to pre-clinical screening tools and clinical evaluation.

7. Joining up maternity care records

Health research in the UK benefits from the NHS' longitudinal health records. However, many health registries do not link up medical data, so information on the effects of medicines cannot be analysed easily. If health records were made accessible through one system, the UK could offer huge potential for following-up the long-term health effects of medicines post-marketing. Better data capture generally would also be helpful, including data on miscarriages, maternal and baby outcomes and electronic prescribing during pregnancy.

A joined-up health data network could build on existing infrastructure across the country. The independent, non-profit organisation Health Data Research UK (HDR UK) already joins up health data science, working with public and private partners, across 31 locations nationwide.

A number of 'Health Data Research Hubs', funded by the Government under the Industrial Strategy Challenge Fund are designated centres of excellence with the expertise to maximise innovations developed from health data across a number of specific contexts, such as eye health, acute care, cancer and respiratory disease. The HDR UK model presents an opportunity to establish a new research hub with a specific focus on using routine clinical maternity data to assess existing and new medicines in pregnancy.

The Commission was convinced of the need to ensure that this aspect of the UK's health sector is supported through appropriate coordination and investment to become truly 'innovation-ready' for pregnancy medicines research.

Recommendation 7

Improve use of routine clinical care maternity data to help assess the safety and effectiveness of new and existing medicines used in pregnancy. Establish a designated maternity 'Health Data Research Hub' through Health Data Research UK with a focus on medicines evaluation in pregnancy.

8. Oversight and delivery

The Commission heard compelling evidence why each of the recommendations highlighted here was vital, both individually but also as part of a mutually-reinforcing approach to creating a position for the UK to drive this vital area forward. However, the individual delivery mechanisms, timescales, necessary stakeholders and markers of success for each of these differs drastically.

A long-term implementation plan is therefore needed to drive forward and oversee developments in this area. Ideally, a Government-appointed group (along the lines of a 'National Steering Committee') representing stakeholders from the public, industry, clinical, academic and regulatory spheres would have the resources and executive power to effect meaningful change.

Implementation needs to align with the Government's recently published Women's Health priorities to ensure a holistic UK approach to women's health across the life course.

The Commission was convinced that women with experience of pregnancy complications should be central to the establishment and delivery of this group.

This group should be formally tasked with driving forward the implementation of the recommendations of this report; monitoring progress against agreed targets; and also developing links internationally to ensure that the UK's leadership delivers true global benefits.

Recommendation 8

Appoint a UK Steering Committee aligned to the Government's Women's Health Strategy to deliver the above recommendations, with oversight of implementation, ensuring milestones are set and monitored.

Conclusions

There is an urgent need for action to address the underserved area of medicines use in pregnancy. Without it, women and babies will continue to die when they could be saved. They will continue to experience long-term health effects, disability and distress, which might be avoided. It is no longer ethical to deny pregnant women and their unborn babies access to safe, modern medicines that the rest of the population enjoys.

We strongly urge that the wide array of stakeholders identified here across the public, scientific, clinical, industry, regulatory and governmental sectors, come together to address the recommendations of this Commission. That together they advocate for change, respond to research and funding issues, and, where necessary, work to change official guidance or law to enable progress in this much neglected area.

As well as the individual costs, investment into safe and effective medicines in pregnancy could save tremendous societal and economic costs: not least because the health of a mother affects the health of her baby, and the health of her baby's babies. Health in pregnancy reverberates down the generations. By boosting generational health, we can boost population health, and thereby the country's overall health, wellbeing and prosperity.

The UK is well placed to become a global pioneer of maternal health research innovation. We have the health infrastructure of our NHS, with its birth-to-death records. Our medicines regulator is able to fast-track drug development and make changes to streamline the process, as well as working globally with Europe, the US and other regions. We are already a global hub for insurance – and we can support and build on this to add to our potential in becoming a leader in clinical studies for medicines in pregnancy.

Now is the time to act – but we will need leadership and investment. With a long-term, cross sector implementation plan we can bring the area of safe, effective and accessible medicines for use in pregnancy into the 21st century. We can save lives, save money, and boost the wellbeing of mothers and babies in the UK and across the world.

‘My risk of having heart disease depends partly on my lifestyle now but also on the quality of the egg from which I grew. And the quality of that egg was determined when my mother was in utero herself. And she was born in 1922 - so that’s 100 years ago.’

Professor Graham Burton, University of Cambridge

Appendices

Appendix 1: Commission Work Programme

Scoping Phase Activities

- Developing the idea for the Policy Commission with University of Birmingham and Birmingham Health Partners.
- Literature review of research and data in the public domain.
- Production and dissemination of 'Safe and Effective Medicines for Use in Pregnancy: A Call to Action' report.
- Appointing the commissioners.
- Commissioners' initial roundtable to agree the terms of reference and decide which expert witnesses to approach for evidence.

Evidence Sessions

Six evidence stakeholder focused sessions were held, followed by a commission summary meeting to agree recommendations.

- Session 1 – Patient Groups, 21st September 2021, Royal College of Physicians, London
- Session 2 – Industry, 22nd September 2021, Royal College of Physicians, London
- Session 3 – Researchers, 19th October 2021, Royal College of Physicians, London
- Session 4 – Practitioners, 20th October 2021, Royal College of Physicians, London
- Session 5 – Litigation and Regulatory Experts, 16th November, The Academy of Medical Sciences, London
- Session 6 – MHRA & Insurance, 17th November, The Academy of Medical Sciences, London

Review and Writing Phase

Activities included:

- Reviewing oral and written evidence submitted to the commission.
- Commissioners' meeting to finalise the content and format of the report.
- Finalising the findings and recommendations of the commission.

2. Commissioners' biographies

Baroness Manningham-Buller, LG, DCB, FMedSci
House of Lords
Co-President, Chatham House

Eliza Manningham-Buller was Chair of Wellcome Trust from 2015 to April 2021, having served as a Governor since 2008. In 2015, Eliza became the Co-President of Chatham House, Royal Institute of International Affairs. She served on the Council of Imperial College from 2009 and was Chair of Council from 2011 to 2015.

She was appointed an independent, crossbench peer in the House of Lords in 2008, has been a member of the Privileges and Conduct Committee and the Joint Committee on the National Security Strategy, and is currently a member of the Science and Technology Committee.

Previously, Eliza had a career with MI5 for more than 30 years, including a posting to the British Embassy in Washington. She served as Director General from 2002 to 2007 and before that was Deputy Director General, with responsibility for operations.

Eliza was educated at Benenden School and Lady Margaret Hall, Oxford. She taught English for three years before joining MI5 in 1974.

Professor Peter Brocklehurst MBChB, MSc, FRCOG, FFPH, FMedSci, Professor of Women's Health, Director of Research and Development, Birmingham Clinical Trials Unit

Peter Brocklehurst is Professor of Women's Health, and Director of Research and Development at the Birmingham Clinical Trials Unit, at the University of Birmingham. Peter trained as an Obstetrician and Gynaecologist and is honorary consultant in Public Health. His expertise is in randomised controlled trials and observational epidemiology.

Previously Peter was Director of the Institute for Women's Health at UCL (2011-2016) where he was Professor of Women's Health, and before that Director of the National Perinatal Epidemiology Unit at the University of Oxford (2002-2011) where he was Professor of Perinatal Epidemiology. He has Chaired or been a member of several funding panels (including the DH Policy Research Programme Commissioning Board; NIHR HTA Commissioning Board; Wellbeing of Women Research Advisory Group; MRC Methodology Research Programme panel). He currently Chairs the UKCRC Pregnancy Research Review Group. He is a Fellow of the Academy of Medical Sciences, and emeritus NIHR Senior Investigator.

Dr Allyah Abbas-Hanif, Chair of the Policy and Communications Group, Faculty of Pharmaceutical Medicine, Royal College of Physicians

Dr Allyah Abbas-Hanif is a consultant in pharmaceutical medicine and a specialist doctor in cardiology. She is Head of Clinical Development at MirZyme Therapeutics, a pregnancy specific biotech. Her academic role of Honorary Senior Clinical Lecturer at Imperial College London allows her to expand policy and research to improve drug development processes for underserved groups. She trained at the University of Birmingham and Yale University.

Allyah is the Chair of the Policy and Communications Group at the Faculty of Pharmaceutical Medicine, Royal College of Physicians. She co-chairs the Paediatric and Women's Health Group at the Faculty of Pharmaceutical Medicine and also co-chairs the Maternal Health Project Group at the Association of the British Pharmaceutical Industry. She sits on Expert Groups focusing on Covid drug development and clinical trial innovation.

Allyah supports several philanthropic projects and is a trustee of the Better Community Business Network. She has led cardiology and emergency medical relief projects for displaced people for international NGOs including the Syrian American Medical Society.

Professor Anna David, Director of the Institute for Women's Health, University College London, Honorary Consultant, Obstetrics and Maternal Fetal Medicine, UCL Hospital, National Institute for Health and Care Research, University College London Hospitals Biomedical Research Centre

Anna is Director of the Elizabeth Garrett Anderson Institute for Women's Health at University College London in London and an Honorary Consultant in Obstetrics and Maternal Fetal Medicine at UCL Hospital. Clinically, she specializes in fetal medicine, severe congenital disease, fetal growth restriction and prevention of preterm birth. Her research team is developing novel prenatal therapies using stem cells and gene therapy. She coordinated the introduction of fetal surgery for spina bifida to the UK in 2018 and co-leads the UCL Centre for Prenatal Therapy.

Anna leads a European Commission FP7 funded consortium 'EVERREST' translating an adenovirus vector maternal growth factor gene therapy for severe fetal growth restriction into the clinic. This 6-year program explored the bioethics of gene therapy in pregnancy, conducted preclinical efficacy and reproductive toxicology studies and developed a first-in-woman clinical trial protocol. Anna also leads UCL as a partner in a European Commission Horizon 2020 funded consortium 'BOOSTB4', that has regulatory and ethical approval to perform the first clinical trial of in utero stem cell transplantation for osteogenesis imperfecta, a severe congenital skeletal dysplasia. She led a Delphi consensus process that generated MFAET, the first system to define and grade maternal and fetal adverse events for clinical trials in pregnancy.

Dr Christine Ekechi, Consultant Obstetrician & Gynaecologist, Queen Charlotte's & Chelsea Hospital, Imperial College Healthcare NHS Trust, Women's Health Educator and Advocate

Dr Ekechi is the Co-Chair of the Race Equality Taskforce at the Royal College of Obstetricians & Gynaecologists and also their spokesperson for racial equality. Her interest is in the gender and racial disparities continually present within the health system today. In addition, Dr Ekechi is the RCOG Clinical Champion for The Women's Network. Dr Ekechi sits as a Member on the Maternity Working Group for the NHS Race and Health Observatory. She also sits on the board as a Trustee for gynaecology cancer charity, The Eve Appeal, and is their Medical Ambassador.

Dr Ekechi is equally focussed on maternity safety and serves as a member of the Multi-Professional Advisory Panel for Baby Lifeline – a UK charity focused on the supportive care of pregnant women and newborn babies. She holds a Masters in Reproductive Health Research from the London School of Hygiene and Tropical Medicine and her previous public health experience includes working with the UN, UNICEF, and national governments in the UK, Nigeria, Senegal, Malawi and Kenya. Using this extensive experience, Dr Ekechi is particularly interested in the social drivers that underpin inequity in individual health outcomes, health knowledge and education, and healthcare delivery.

Dr Ekechi curates and delivers women's health education seminars for corporate companies, charities and interested groups, empowering all women to better manage their health. Dr Ekechi uses her various platforms to discuss all subjects in women's health whilst also calling for greater awareness from women, clinicians and other agencies in improving women's health outcomes.

Dr Ekechi is the lead for early pregnancy ultrasound training at the renowned early pregnancy unit at Queen Charlotte's Hospital and regularly teaches and writes in this field. She also practices at The Portland Hospital, the largest private women's and children's hospital in the UK. Dr Christine Ekechi is the Founder and Director of Early Pregnancy Plus, an innovative holistic early pregnancy care service in central London.

Marcus Green, Chief Executive, Action on Pre-Eclampsia (UK)

Marcus is the part time CEO of APEC, a role he's held since June 2016. He's led the development of the research programme where he's placed a strong emphasis on patient voices. He has also been involved in international developments with the charity including APEC International and APEC Ghana.

Marcus's career started in working for a political party where he worked on local, national and European polls as well as election observing in Albania, campaigning in Malawi and lecturing in Eastern Europe as part of the Westminster Foundation for Democracy.

After this Marcus started his career in charities where his first director role was with a charity for the visually impaired before becoming CEO of a hospice. In the 4.5 years he was there, he oversaw the building of a new hospice, a doubling of turnover, and a tripling of patients.

Marcus then set up his own Management Consultancy specialising in supporting leadership teams, boards and CEOs. Marcus's interest in pre-eclampsia came after his wife suffered with it, 13 years ago. Outside of work, Marcus was the Cathedral Photographer for the best-selling *Britain's Pilgrim Places* is on the Council of The Friends of Gloucester Cathedral, is studying for an MBA, writing another book, and chairs a computer software development company.

Dr A. Metin Gülmezoglu, Executive Director, Concept Foundation

Dr A. Metin Gülmezoglu is an Obstetrician Gynaecologist who has worked in Turkey, South Africa, and the United Kingdom and is currently working in Geneva, Switzerland. Metin is the Executive Director of Concept Foundation, a nonprofit non-governmental organisation working on improving access to sexual and reproductive health medicines and technologies in low- and middle-income countries worldwide.

Prior to joining Concept Foundation, Metin worked at the World Health Organization, as the Coordinator for Maternal and Perinatal Health and Abortion from 2013 until mid-2019. Since the mid-1990s, Metin has worked as a sexual and reproductive health researcher within the global health environment. Metin's own research focuses on major causes of maternal death.

He has coordinated large, multicenter, multicountry randomised controlled trials during his time at the WHO and led a highly successful public private partnership between the WHO, Merck for Mothers, and Ferring Pharmaceuticals, evaluating the effectiveness of heat stable carbetocin. In addition to his thematic research interests, Metin has always had an interest in research methodology, good research practice and mentoring young researchers, especially those from low- and middle-income countries.

Metin has published more than 300 articles and book chapters and given numerous presentations in global, regional and national conferences and meetings. Metin is an honorary fellow of the Royal College of Obstetricians and Gynaecologists in the UK and honorary member of The Society for Maternal Fetal Medicine in the USA.

Mark Hilton, Intellectual Property Group Partner, Bird & Bird Co-head of International Life Sciences and Healthcare Group

Mark is a partner in Bird & Bird's leading international intellectual property group, based in London. As one of the team's pre-eminent litigators, he has particular experience advising on complex multi-jurisdictional IP disputes. Mark is also co-head of the international Life Sciences and Healthcare group and specialises in patent litigation and Life Sciences regulatory advice in the area of pharmaceuticals, biosimilars, biotechnology and medical devices.

In the course of over 20 years of experience of patent litigation, Mark has been involved in devising successful litigation strategies and co-ordinating complex multi-jurisdictional disputes for clients, which often include the interplay of patent and regulatory protections. He is keen to advance the use of technology to improve the delivery of these services to clients and has developed various IT solutions to improve information exchange and make significant improvements to productivity. In particular, Mark has led a project to develop an online patent litigation management tool that allows clients immediate access to the status of all of their litigation, efficient communication of instructions and budget control, while at the same time reducing the overall cost of the litigation.

Mark has a BSc in Chemistry and a PhD in Organic Chemistry, which he obtained while working in the industry before undertaking training with Bird & Bird. He has written and spoken on a range of IP topics, is an associate of the Chartered Institute of Patent Attorneys (CIPA) and a member of the Law Society of Ireland.

Steve Hoare, Quality, Regulatory Science & Safety Policy Director, The Association of the British Pharmaceutical Industry (ABPI)

An analytical chemist by training, Steve Hoare had a career leading quality functions within the pharmaceutical industry. His experience covers the full lifecycle of medicines from early drug discovery through to manufacture and supply.

In his current role, Steve leads policy development in Regulatory Science for the Association of the British Pharmaceutical Industry and is the ABPI regulatory lead for their Maternal Health Project Group, which comprises industry, academia, clinicians, regulators, and patients. The remit for this Project Group is to improve the number of medicines/therapies available to prescribe during pregnancy, through reducing barriers to inclusion of pregnant women in clinical trials, and to address data gaps in both research and post-marketing of medicines.

Appendix 3: The Witnesses

Jane Brewin
CEO, Tommy's

Eleni Tsigas
CEO, Preeclampsia Foundation

Clea Harmer
Chair, Pregnancy and Baby Charities Network

Sarah McMullen
Director of Impact and Engagement, NCT

Dr Pauline Williams
Senior Vice President, Head of Global Health R&D, GlaxoSmithKline Medicines Research Centre

Dr Mirjam Mol-Arts
Executive Vice-President, Chief Medical and Science Officer, Ferring Pharmaceuticals

Gisela Abbam
Senior Director, Government Affairs, PerkinElmer Inc, Chair of British Science Association and Member of the Advisory Board, Everywoman Ltd.

Dr Flic Gabbay
President, Faculty of Pharmaceutical Medicine and CEO Transcript

Prof Amin Rostami-Hodjegan
Director of the Centre for Applied Pharmacokinetic Research (CAPKR). Senior Vice President of R&D and Chief Scientific Officer, Certara

Professor Mark Turner
Professor of Neonatology and Research Delivery, University of Liverpool

Professor Jane Norman
Dean, Faculty of Health Sciences, University of Bristol

Professor Graham J Burton
Mary Marshall and Arthur Walton Professor Emeritus of the Physiology of Reproduction, University of Cambridge

Professor Steve Cunningham
Professor of Paediatric Respiratory Medicine, University of Edinburgh and Chair of the MHRA Paediatric Medicines Expert Advisory Group

Professor Neena Modi
President of the British Medical Association, Professor of Neonatal Medicine, Imperial College London, and Trustee of Their World

Dr Matthew Jolly
National Clinical Director for the Maternity Review and Women's Health, NHS England

Professor Catherine Nelson-Piercy
Professor of Obstetric Medicine and Consultant Obstetric Physician, Guy's and St Thomas' NHS Foundation Trust

Gill Walton
Chief Executive, Royal College of Midwives

Professor Richard Ashcroft
Deputy Dean and Professor of Bioethics, City Law School

Professor Corinne de Vries
Head of Science and Innovation Support, Human Medicines Research & Development Support Division, European Medicines Agency

Dr Sabine Straus
Chair, Pharmacovigilance Risk Assessment Committee (PRAC), European Medicines Agency

Professor Dame Lesley Regan DBE MD DSc FRCOG
Head, Department of Obstetrics & Gynaecology and Chair of Wellbeing of Women

Dame June Raine DBE
Chief Executive, MHRA

Dr Janet Nooney
Expert Scientific Assessor, MHRA

Rob Hannaford
Insurance Underwriter, Newline Group

Ben Ward
Insurance Underwriter, Newline Group

Gary Priest
Risk and Insurance (Research) Lead, University of Oxford

Nathan Draper
Policy and Public Affairs Manager, the Epilepsy Society

Appendix 4: References

Berezow A. Clinical Trial Success Rates By Phase And Therapeutic Area. American Council on Science and Health. June 2020 **https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845**

Bhattacharya S. on behalf of Birmingham Health Partners Centre for Regulatory Science and Innovation, Safe and Effective Medicines for Use in Pregnancy: A Call to Action, January 2021

Chappell LC, David AL. 2016. 'Improving the Pipeline for Developing and Testing Pharmacological Treatments in Pregnancy.' *PLOS Medicine 13 (11): e1002161* **https://doi.org/10.1371/journal.pmed.1002161**

Cooksey, D. A review of UK health research funding. December 2006 **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf**

Eichler HG, Abadie E, Baker M, Rasi G. Fifty years after thalidomide; what role for drug regulators? Br J Clin Pharmacol 2012; 74: 731–3.

End Violence Against Women. Our members. [Accessed 30/3/22] **https://www.endviolenceagainstwomen.org.uk/about/our-members/**

Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018 Sep; 11: 156–164. Published online 2018 Aug 7. doi: 10.1016/j.conctc.2018.08.001

Gov.UK. 'Call to end violence against women and girls'. 25 November 2010. **https://www.gov.uk/government/publications/call-to-end-violence-against-women-and-girls [Accessed 30/3/22]**

Gov.UK. 'Covid-19 vaccination: a guide on pregnancy and breastfeeding'. **https://www.gov.uk/government/publications/Covid-19-vaccination-women-of-childbearing-age-currently-pregnant-planning-a-pregnancy-or-breastfeeding/covid-19-vaccination-a-guide-for-women-of-childbearing-age-pregnant-planning-a-pregnancy-or-breastfeeding [Accessed 20/1/22]**

Gov.UK. 'Innovative Licensing and Access Pathway'. **https://www.gov.uk/guidance/innovative-licensing-and-access-pathway [Accessed 25/1/22]**

Gov.UK. 'Safer Medicines in Pregnancy and Breastfeeding Consortium'. **https://www.gov.uk/government/publications/safer-medicines-in-pregnancy-and-breastfeeding-consortium [Accessed 28/1/22]**

Gov.UK. 'Strategy to end violence against women and girls: 2016 to 2020'. 8 March 2016. **https://www.gov.uk/government/publications/strategy-to-end-violence-against-women-and-girls-2016-to-2020 [Accessed 30/3/22]**

Gov.UK. 'Tackling violence against women and girls'. 21 July 2021. **https://www.gov.uk/government/publications/tackling-violence-against-women-and-girls-strategy [Accessed 30/3/22]**

Gov.UK. 'Taskforce on Innovation, Growth and Regulatory Reform independent report'. 16 June 2021 **https://www.gov.uk/government/publications/taskforce-on-innovation-growth-and-regulatory-reform-independent-report [Accessed 25/1/22]**

Health Data Research UK. 'Who Are We?' **https://www.hdruk.ac.uk/about-us/ [Accessed 20/1/22]**

Herring C, McManus A, Weeks A. 2010. 'Off-Label Prescribing during Pregnancy in the UK: An Analysis of 18,000 Prescriptions in Liverpool Women's Hospital.' *International Journal of Pharmacy Practice* 18 (4): 226–29. **https://onlinelibrary.wiley.com/doi/abs/10.1211/ijpp.18.04.0007**

Hoover RN. et al. *'Adverse health outcomes in women exposed in utero to diethylstilbestrol.'* N. Engl. J. Med. 365(14), 1304–1314, **https://doi.org/10.1056/NEJMoa1013961** (2011). Jakes AD, Watt-Coote I, Coleman M, Nelson-Piercy C. 2016. 'Obstetric medical care and training in the United Kingdom.' Obstetric Medicine 10 (1): 40–42.

Lintern S. 'Family wins £37m in one of the largest maternity negligence claims in NHS history'. The Independent. July 2020. **https://www.independent.co.uk/news/health/maternity-safety-nhs-negligence-guys-thomas-a9357501.html**

Mangham LJ, Petrou S, Doyle LW, Draper ES, Marlow N. 2009. 'The Cost of Preterm Birth Throughout Childhood in England and Wales.' Pediatrics 123 (2): e312–27. **https://doi.org/10.1542/peds.2008-1827**

MBBRACE-UK. 'Saving Lives, Improving Mothers' Care: Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18'. December 2020. **https://www.npeu.ox.ac.uk/assets/downloads/mbrrace-uk/reports/maternal-report-2020/MBRRACE-UK_Maternal_Report_Dec_2020_v10_ONLINE_VERSION_1404.pdf**

Medley N, Vogel JP, Care A, Alfirevic Z. 'Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews.' Cochrane Database Syst. Rev. 2018;11:CD012505 Published online 2018 Nov 14. doi: 10.1002/14651858.CD012505.pub2

NHS England. 'NHS encourages pregnant women to get Covid-19 vaccine'. 11 October 2021. **https://www.england.nhs.uk/2021/10/nhs-encourages-pregnant-women-to-get-covid-19-vaccine/ [Accessed 20/1/22]**

Pool Re. **https://www.poolre.co.uk/about/ [Accessed 25/1/22]** and **https://www.poolre.co.uk/cover/ [Accessed 6/3/22]**

Public Health England. 'National Congenital Anomaly and Rare Disease Registration Service: Congenital anomaly statistics 2018'. August 2020. **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1008030/NCARDRS_Congenital_anomaly_statistics_report_2018.pdf**

RAND Europe. 'Pregnancy Research Review: Policy Report'. 2020
RECOVERY. 'Randomised Evaluation of COVID-19 Therapy (RECOVERY) for Pregnant and Breastfeeding Women'. **https://www.recoverytrial.net/files/recovery-in-pregnant-women-for-hcp-v15-1-2021-12-22.pdf/@@download [Accessed 20/1/22]**

Royal College of Obstetricians & Gynaecologists. 'COVID-19 vaccines, pregnancy and breastfeeding' guidance. **https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/covid-19-vaccines-and-pregnancy/covid-19-vaccines-pregnancy-and-breastfeeding/ [Accessed 20/1/22]**

SANDS. Sands and Tommy's joint policy unit. **https://www.sands.org.uk/joint-policy-unit**

United Nations Inter-Agency Group for Child Mortality Estimation, Report 2021. Levels and trends in child mortality 2021

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