

First Do No Harm

The report of the Independent Medicines and Medical Devices Safety Review





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Letter to the Secretary of State from Baroness Cumberlege

8th July 2020

Dear Secretary of State

I publish this report at a time when the NHS has been facing enormous challenges arising from the Covid-19 pandemic. NHS staff have risen to those challenges, proving day after day their ability to provide excellent care often in the most testing of circumstances. All of us have, quite literally, applauded them for their tireless commitment.

This Review, however, has been about people who have suffered avoidable harm. Our report is entitled “First Do No Harm”. Having spent two years listening to heart wrenching stories of acute suffering, families fractured, children harmed and much else, I and my team thought it an appropriate title. It is a phrase that should serve as a guiding principle, and the starting point, not only for doctors but for all the other component parts of our healthcare system. Too often, we believe it has not.

Throughout I have valued the commitment, wise advice and integrity of Sir Cyril Chantler and Simon Whale. The three of us were the Review Panel and the decision makers. Dr Valerie Brasse, our gifted secretary, led the small support team to whom we are hugely grateful.

The three areas we were asked to explore, Primodos, sodium valproate and pelvic mesh, were new to us so we travelled the country, not only England but Scotland, Wales and Northern Ireland. We met and listened to over 700 people, mostly women, often accompanied by their partners, other family members and sometimes their children. We are indebted to all of them. Their dignity and courage in telling us intimate and harrowing details of their damaged lives has made a great and lasting impression on us.

The patient groups, some of whom have campaigned for decades, have been invaluable to us; well informed, knowledgeable, and research based. They never failed to ensure we learnt from them and were up to date with emerging developments. They are outstanding communicators and expert in the subject matter.

We have found that the healthcare system – in which I include the NHS, private providers, the regulators and professional bodies, pharmaceutical and device manufacturers, and

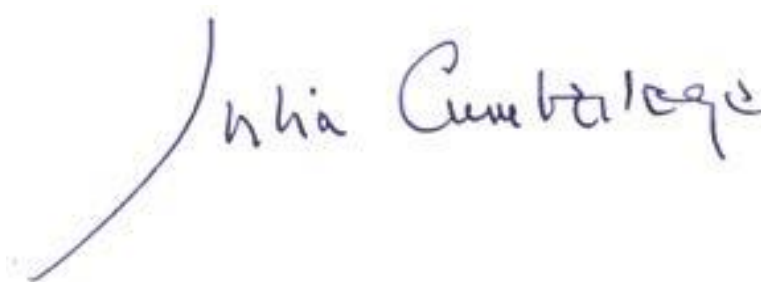
policymakers – is disjointed, siloed, unresponsive and defensive. It does not adequately recognise that patients are its *raison d'être*. It has failed to listen to their concerns and when, belatedly, it has decided to act it has too often moved glacially. Indeed, over these two years we have found ourselves in the position of recommending, encouraging and urging the system to take action that should have been taken long ago.

The system is not good enough at spotting trends in practice and outcomes that give rise to safety concerns. Listening to patients is pivotal to that. This is why one of our principal recommendations is the appointment of an independent Patient Safety Commissioner, a person of standing who sits outside the healthcare system, accountable to Parliament through the Health and Social Care Select Committee. The Commissioner would be the patients' port of call, listener and advocate, who holds the system to account, monitors trends, encourages and requires the system to act. This person would be the golden thread, tying the disjointed system together in the interests of those who matter most.

Secretary of State, we are entering a new world, in which innovation and technology will bring exciting change. There is potential to do so much good, but we must ensure the risks of increasingly complex healthcare are understood and where the system is not sure of the risks it must say so. Had it done so in the case of our three interventions, I have no doubt that much anguish, suffering and many ruined lives could have been avoided.

My team and I are clear that our recommendations will improve the lives of people who have been harmed and make the system safer in the future. Implementation needs to be approached with a new urgency and determination, founded on the guiding principle that our healthcare system must first do no harm.

Yours sincerely,

A handwritten signature in blue ink, reading "Nicola Cumberlege". The signature is written in a cursive style, with a large, sweeping initial 'N'.

Acknowledgements

This report and all the work that led to it would not have been possible without the advice, support and knowledge of numerous individuals and organisations.¹

First and foremost, I wish to thank all those people affected by the medical interventions we examined who met with us and had contact with us in writing and by telephone. It has been vital for us to hear their stories and understand their concerns. I am acutely aware that sharing such painful experiences with us has been traumatic for many, but my team and I are immensely grateful to each and every one of them. We heard their voices, and we listened.

I pay a special tribute to all of the patient groups for their insight and support throughout this Review. Their knowledge of these medical interventions and the effect they have had on those they represent is extraordinarily comprehensive. The support they provide to those who have suffered is quite remarkable, all the more so given that many of the groups are led by people who have themselves suffered harm.

I wish to thank everyone who gave us evidence in writing, appeared at our oral hearings and provided information to us through the course of the Review. We appreciate the time and expertise of everyone concerned, and the willingness with which it was given to us.

And Sir Cyril Chantler, Simon Whale and I wish to thank our talented secretariat team, led so ably by Dr Valerie Brasse. This small team has managed a sensitive, complex and demanding task with enthusiasm, good humour and complete dedication. They have been truly exceptional, and we owe them a great debt of gratitude.

¹ Further information on the patient groups the Review team interacted with, on those who provided written and/or oral evidence during the course of the Review and the members of the Independent Medicines and Medical Devices Safety Review team can be found in Appendix 5.

How to read the report

Chapter 1 provides a summary of our findings and our Recommendations. Chapter 2 considers overarching themes relevant to all three of the interventions the Review was asked to look at. Chapters 3, 4, and 5 consider these interventions in more detail. Throughout these chapters are 'Actions for Improvement'. Chapter 6 considers the role of public inquiries. In chapter 7 we present our suggestions for driving forward implementation, and chapter 8 is a summary of our Recommendations and Actions for Improvement.

More detail related to our Recommendations can be found in the Appendices. We also have online resources which support this report.

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1 Introduction and Overview

*'It is an essential principle of patient safety that the regulatory environment gives sufficient voice to legitimate concerns reported by patients, families and campaigners, works alongside them and responds in a rapid, open and compassionate way to resolve issues when they are raised. My view is that that did not happen in the way I would expect in these three cases.'*²

Rt Hon Jeremy Hunt MP, former Secretary of State for Health and Social Care

- 1.1 This Review was announced in the House of Commons on 21st February 2018 by Jeremy Hunt, the then Secretary of State for Health and Social Care. Its purpose is to examine how the healthcare system in England responds to reports about harmful side effects from medicines and medical devices and to consider how to respond to them more quickly and effectively in the future.³
- 1.2 Under my chairmanship the Review was asked to investigate what had happened in respect of two medications and one medical device:
 - hormone pregnancy tests (HPTs) – tests, such as Primodos, which were withdrawn from the market in the late 1970s and which are thought to be associated with birth defects and miscarriages;
 - sodium valproate – an effective anti-epileptic drug which causes physical malformations, autism and developmental delay in many children when it is taken by their mothers during pregnancy; and
 - pelvic mesh implants – used in the surgical repair of pelvic organ prolapse and to manage stress urinary incontinence. Its use has been linked to crippling, life- changing, complications;

and to make recommendations for the future.
- 1.3 The Review was prompted by patient-led campaigns that have run for years and, in the cases of valproate and Primodos over decades, drawing active support from their respective All-Party Parliamentary Groups and the media.

² Secretary of State for Health's statement to the House of Commons, 21st February 2018. <https://hansard.parliament.uk/commons/2018-02-21/debates>

³ *ibid.*

1.4 As the Secretary of State commented:

*'We must acknowledge that the response to these issues from those in positions of authority has not always been good enough. Sometimes the reaction has felt too focussed on defending the status quo, rather than addressing the needs of patients and, as a result, patients and their families have spent too long feeling that they were not being listened to...'*⁴

1.5 The Review was asked to consider how to strengthen the patient voice in order to help build a *'system that listens, hears and acts – with speed, compassion and proportionality.'*⁵

1.6 On the face of it we were being asked to investigate three disparate interventions governed by two different product regulatory frameworks in the one Review. It soon became apparent, however, that far more binds these interventions than separates them:

- they all are taken or used by women and, in the cases of valproate and hormone pregnancy tests, usage is during pregnancy;
- patients affected by each tell similar and compelling stories of their battles to be listened to when things go wrong;
- patients turning to each other for help and mutual support;
- patients campaigning for years, if not decades, to achieve acknowledgement, resorting to the media and politicians to take up their cause because the healthcare system did not.

1.7 The Review looks not just at what happened in the three individual cases but how the healthcare system reacted as a whole, and how that response can be made more robust, speedy and appropriate. It is in this sense a system-wide review.

1.8 Finally, as complex and wide-ranging as our Review proved to be, we know that there are many who contacted us during the course of our work and who were disappointed that we could not also consider their concerns about other medications and devices on the market. The list is long – Essure (a contraceptive device), Roaccutane (a treatment for severe acne that can cause birth defects if used in pregnancy), Poly Implant Protheses (PIP) breast implants, cervical cancer vaccination, in utero exposure to hormones, valproate use in children. We are

⁴ *ibid.*

⁵ *ibid.*

aware of the similarities between pelvic mesh and mesh used for hernia procedures and we have heard from a number of people adversely affected following hernia mesh procedures. With regards to mesh, the scope of this Review relates only to pelvic mesh, which following insertion resides in the pelvis to support pelvic organs. So, neither hernia mesh nor the other medications and devices listed above were within our remit. Concerns about these taken together, however, point to a healthcare system that cannot be relied upon to identify and respond promptly to safety concerns. We believe that what we have to say and recommend for the future will have an important read-across to these and other interventions and the manner in which they are approved, delivered, regulated and monitored.

- 1.9 What follows is a summary of what we heard, and then a summary of our observations and recommendations and the reasoning behind them. These recommendations cover England only, though we know the devolved administrations are following our work closely. We hope those governments will consider the recommendations we have made for England.

What we heard

- 1.10 Patients were at the heart of our Review. Although our focus was on England, we travelled to the four corners of the UK to listen and learn. We met with hundreds of affected patients and their families and heard by email, phone and letter from many more. It became all too clear that those who have been affected have been dismissed, overlooked, and ignored for far too long. The issue here is not one of a single or a few rogue medical practitioners, or differences in regional practice. It is system-wide.
- 1.11 We took evidence from a wide range of stakeholders, from clinicians and the Royal Colleges, from the pharmaceutical industry and manufacturers of devices, from the full range of NHS and private sector providers and arms-length bodies including the regulators, professional and disciplinary bodies and finally from the Department of Health and Social Care. Collectively we refer to this group of stakeholders as the healthcare system.
- 1.12 The patients' stories were harrowing. Our two-year journey took its toll on all of us but that paled into insignificance in the face of so much adversity borne with such resilience and bravery by those we met and heard from. They told their stories with dignity and eloquence, but also with sadness and anger, to highlight common and compelling themes:
- the lack of information to make informed choices;

- lack of awareness of who to complain to and how to report adverse events;
- the struggle to be heard;
- not being believed;
- dismissive and unhelpful attitudes on the part of some clinicians;
- a sense of abandonment;
- life-changing consequences, not only for those directly affected, but for their families and friends too;
- breakdown of family life;
- loss of jobs, financial support and sometimes housing;
- loss of identity and self-worth;
- a persistent feeling of guilt;
- children becoming their mothers' and siblings' carers;
- clinicians untutored in the skills they need to make a proper diagnosis;
- clinicians not knowing how to learn from patients;
- inaccurate or altered patient records;
- a lack of interest in, and an inability to deliver, the monitoring of adverse outcomes and long-term follow-up across the healthcare system.

1.13 These testimonies provided the background to our own diligent inquiry into the roles played by those whose job it is to *'listen, hear and act with compassion, speed and proportionality'*.⁶

What we learnt

1.14 What follows will not make comfortable reading for many who have dedicated their lives with the best of intentions to delivering high-quality and compassionate treatment and care. We recognise that most people do excellent work most of the time in the health service. They work hard, they work long hours and they came

⁶ Secretary of State for Health's statement to the House of Commons, 21st February 2018. <https://hansard.parliament.uk/commons/2018-02-21/debates>

into the healthcare professions to help sick people get better, never more so than during the Covid-19 pandemic. We recognise too that the constituent parts of the healthcare system do for the most part what each is asked to do. But what they have been asked to do is not the solution to the problem as we see it.

- 1.15 Innovation in medical care has done wonderful things and saved many lives. But innovation without comprehensive pre-market testing and post-marketing surveillance and long-term monitoring of outcomes is, quite simply, dangerous. Crucial opportunities are lost to learn about what works well, what does not, what needs special measures put around its use, and what should be withdrawn because the risks over time outweigh the benefits. Without such information it is not possible for doctors and patients to understand the risks, and patients cannot make informed choices. This applies both to medications and to medical devices.
- 1.16 The lack of such vigilant, long-term monitoring has been a predominant thread throughout our work. Its absence means that the system does not know the scale of the problems we were asked to investigate:
- i. The system does not know, so neither do we, just how many women have been treated for stress urinary incontinence and the repair of pelvic organ prolapse using polypropylene mesh.⁷ The system does not know, so neither do we, how many women have been cured of their incontinence, or been successfully treated for their prolapse – only then to experience a long list of life-changing conditions that include loss of sex life, chronic pain, infection, difficulty voiding, recurrent urinary incontinence, permanent nerve damage or damage to surrounding organs, haemorrhage, autoimmune disease and psychiatric injury.

We met so many women with limited mobility having to rely on a wheelchair or crutches to move around, unable to sit for periods at a time, unable to play with their children or carry their grandchildren. Living daily with the consequences of the operations and procedures they thought would cure them. The effects of these procedures have caused fractured relationships for some and placed some women and their families in dire financial straits. In short, the system does not know the true long-term complication rate for pelvic mesh procedures. In the absence of such

⁷ An experimental NHS retrospective audit of annual HES data on mesh implant procedures published in April 2018 was widely criticised for its omissions e.g. lack of any private sector data and for its implied underestimate of long-term complications. *NHS Digital Retrospective Review of Surgery for Urogynaecological Prolapse and Stress Urinary Incontinence using Tape or Mesh: Hospital Episode Statistics (HES), Experimental Statistics, April 2008 - March 2017*.

information, it is impossible to know how many women would have chosen a different form of treatment – a different care pathway – if only they had been given the information they needed to make a fully-informed choice;

- ii. The system does not know, so neither do we, just how many women over four decades took sodium valproate, a highly effective treatment for managing epilepsy but a known teratogenic medication, who then went on to become pregnant because they had not been properly informed as to the risk they were taking and the options open to them. The system does not know, so neither do we, how many of those children were subsequently born with either significant malformations, developmental delay or autism (now termed Foetal Valproate Spectrum Disorder or FVSD). The research tells us that 10% of unborn children exposed to the medication are likely to suffer physical birth defects such as spina bifida, hare lip and cleft palate, heart problems and limb defects, and 40% will have a developmental delay or autism.⁸ The system still does not know where all these valproate-affected children, now adults in many cases, are, or how to contact them to secure the proper diagnosis and assessment of their care needs. The system does not know how to ensure every woman of childbearing age on sodium valproate is continuously monitored, advised of the risks and aware of the Pregnancy Prevention Programme. How then can the system minimise the risk of future babies being damaged by valproate taken in pregnancy?
- iii. The system does not know, so neither do we, just how many women took a Hormone Pregnancy Test, such as Primodos, between the 1950s and 1978 when it was withdrawn. The system does not know, so neither do we, how many miscarriages may have occurred after taking this medication, how many of the children born to mothers who took Primodos may have suffered physical malformations or died before reaching adulthood, or how many of those children, now adults, may still be alive and in need of extensive care and support.

1.17 The healthcare system collects a huge amount of information. But it cannot answer these fundamental questions. How then can it spot trends and complications and act swiftly and coherently to protect patients and prevent harm? How then can it design and provide the services that those affected need to lead as full a life as possible? How then can the healthcare system be considered a system for all?

⁸ See for example the written submission of Professor Jill Clayton-Smith, Dr Rebecca Bromley, Professor Peter Turnpenny and Professor Amanda G Wood. For further references see Chapter 4 and Annex C Sodium valproate timeline.

- 1.18 We heard about the failure of the system to acknowledge when things go wrong for fear of blame and litigation. There is an institutional and professional resistance to changing practice even in the face of mounting safety concerns. There can be a culture of dismissive and arrogant attitudes that only serve to intimidate and confuse. For women there is an added dimension – the widespread and wholly unacceptable labelling of so many symptoms as ‘normal’ and attributable to ‘women’s problems’.
- 1.19 We heard about a system that does not work in a joined-up fashion, and that lacks the leadership to deliver coherent and fully integrated patient safety policy directives and standards. Mistakes are perpetuated through a culture of denial, a resistance to no-blame learning, and an absence of overall effective accountability. This culture has to change, starting at ground level while being encouraged and supported from the top. Witness Professor Ted Baker, the Care Quality Commission’s (CQC) Chief Inspector of Hospitals, speaking at a recent Patient Safety Learning Conference at The King’s Fund, referring to an *‘insidious culture of defensiveness and blame.’*⁹

‘I have to say 20 years later it is very frustrating how little progress we have made. It’s clear to me that we still have not got the leadership and culture around patient safety right. As long as you have that culture of people trying to hide things - then we are not going to win this.’

Professor Ted Baker, Chief Inspector of Hospitals, CQC

- 1.20 We heard about a system that cannot be relied upon to identify promptly significant adverse outcomes arising from a medication or device because it lacks the means to do so. For decades there has been something known as the ‘Yellow Card’ system through which clinicians, and indeed patients, can report suspected adverse reactions to treatment. But it is clear that there is gross under-reporting, and our complaints systems are both too complex and too diffuse to allow early signal detection.
- 1.21 We heard much said about manufacturers being motivated by sales, speed to market and returns to shareholders; manufacturers who contest their liability to contribute towards help for these patient groups. Those suffering from mesh complications around the world have had to resort to litigation to have the wrongs done to them acknowledged. Valproate-affected families have also failed in their group litigation attempt in the UK. In France it is a government-backed scheme that will pay compensation to those who have suffered one or more complications

⁹ The Patient Safety Learning Conference, King’s Fund, October 2019.

attributable to Fetal Valproate Spectrum Disorder. HPT-affected families in the UK have one failed litigation behind them although we understand that solicitors are now preparing to file a second group action in the UK in relation to HPTs.¹⁰

- 1.22 We heard about the gaps in knowledge and evidence gathering that have already been identified by the National Institute for Health and Care Excellence (NICE), and by others who set the standards for best clinical practice. Crucial research evidence that should help shine a light on what are safe and effective interventions is neither prioritised nor funded. And we heard about research that is funded by manufacturers that never sees the light of day because it is negative or inconclusive for the product in question, or is less than transparent in its declaration of conflicts of interest when positive findings are reported.
- 1.23 All that we have heard leads us to conclude the system is not safe enough for those taking medications in pregnancy or being treated using new devices and techniques. Patients are being exposed to a risk of harm when they do not need to be. And, while we have looked in detail at only three interventions, we have heard nothing that would lead us to believe that things are different for other surgical procedures and devices or other medications.
- 1.24 It has taken this Review to shine a light on systemic failings. That the healthcare system itself failed to do so suggests that it has either lost sight of the interests of all those it was set up to serve or does not know how best to do this. The NHS is funded by the taxpayer for the benefit of all of society – current and future. Patients have been affected adversely by poor or indifferent care, have suffered at the hands of clinicians who do not, or who chose not to listen, and have been abandoned by a system that fails to recognise and then correct its mistakes at the earliest opportunity. At times patients have been denied their fundamental right to have the information they need to make fully informed choices. These patients should not have to campaign for years or even decades for their voices to be heard. Patients should not have to find the evidence to say whether the treatments they are being offered are safe and will leave them better off than before. They should not have to join the dots of patient safety. But when they do just that, they deserve to be listened to with respect.
- 1.25 Medicine has made great strides in what it has been able to do to prolong life and treat the previously untreatable. But along that journey of scientific progress it has also become complex and potentially too dangerous to be left solely in the hands

¹⁰ For example the most recent Australian judgment in *Gill v Ethicon Sarl* (No5) [2019] FCA 1905; the Primodos Action Group set up by SPG Law, <https://www.spglaw.co.uk/primodos-case/>; and reference to the French scheme for valproate affected families in Chapter 4 paragraph 4.88. See Appendix 3 – Redress paper for more detail.

of clinicians. The influence of patients within the NHS and the overall delivery of healthcare needs to be increased to balance the authority both directly and indirectly of those we call stakeholders in the healthcare system – the professionals certainly, but others too, including big pharma. Patients are unable to make decisions that concern what happens to them because of a widespread lack of truly informed consent and a reluctance or inability by those charged with patient care and treatment to listen and, having listened, to act and where necessary remedy mistakes or misjudgements made. We have much more to say about this throughout our report.

- 1.26 In the following chapters we catalogue a list of missed opportunities. These are moments when something could or should have been done to minimise continuing patient harm in respect of each of the three interventions. We also set out our recommendations below and the justification for them.
- 1.27 Many will have benefited from pelvic mesh implants. Likewise, sodium valproate will have been an effective treatment for many. But this cannot justify the damage done to those who have suffered without prior knowledge of the dangers they faced – which could take years to present. While the title of our report may not be original, it was chosen with care. ‘FIRST DO NO HARM’ is a fundamental maxim of medical practice – and that has not been the case here. After ‘first do no harm’ comes, of course, ‘NEXT DO SOME GOOD’. We do not want to stifle the medical progress which has enabled many of us to live longer and in better health over the last fifty years. The task for the healthcare system is to get the balance right. It can and must do both.

Our Recommendations

- 1.28 Our Terms of Reference required us to investigate whether the response of the healthcare system was sufficiently robust, speedy and appropriate. In the following chapters we will show that it was not, resulting in avoidable harm. The passage of time between the concerns being raised and the effectiveness of actions taken to address those concerns and then to investigate and learn the lessons – decades in the case of sodium valproate and Primodos – demonstrably added to the suffering and pain of those affected. The system, and those that oversee it, need to acknowledge what has gone so badly wrong.

Recommendation 1: The Government should immediately issue a fulsome apology on behalf of the healthcare system to the families affected by Primodos, sodium valproate and pelvic mesh.

- 1.29 The patient voice and influence within the NHS and the overall delivery of health care needs to be strengthened. The failure of the healthcare system to respond to patient concerns is a recurrent theme, most recently raised by the Paterson Inquiry.¹¹ Patients often know when something has gone wrong with their treatment. All too often they are the first to know. Their experience must no longer be considered anecdotal and weighted least in the hierarchy of evidence-based medicine.¹²
- 1.30 We do not need another re-organisation of the NHS to get this right; we do not need another regulatory body in an already crowded field. But we do need a new voice, with statutory powers, to talk and act from the perspective of the patient, to encourage the system to do what needs to be done and hold it to account. We need a person of standing who sits outside the healthcare system and who is accountable to Parliament through the Health and Social Care Select Committee. This new voice, which we are calling the Patient Safety Commissioner, would continue the work this Review has started, in pressing the system to take timely action where action is called for to minimise harm.
- 1.31 This new Commissioner would champion the patient voice and from this unique perspective would support and encourage the efforts of the healthcare system to improve patient safety around the use of medicines and medical devices. The Commissioner would lead, with full patient group engagement and involvement, on developing a set of principles of Better Patient Safety that would govern the way the Commissioner fulfilled her or his remit.
- 1.32 Where there are areas of concern related to the use of medicines and devices, the healthcare system will need to satisfy the Patient Safety Commissioner on the outcomes required for change, who is responsible for delivery and who will take the lead on co-ordination. The Patient Safety Commissioner will wish to monitor the effectiveness of the outcomes.

Recommendation 2: The appointment of a Patient Safety Commissioner who would be an independent public leader with a statutory responsibility. The Commissioner would champion the value of listening to patients and promoting users' perspectives in seeking improvements to patient safety around the use of medicines and medical devices.¹³

¹¹ Report of the Independent Inquiry into the Issues raised by Paterson (February 2020) available at <https://www.gov.uk/government/publications/paterson-inquiry-report>

¹² See Rawlins Michael. *De testimonio*: on the evidence for decisions about the use of therapeutic interventions, Harveian Oration, The Lancet Vol 372, December 20/27, 2008:2152-61

¹³ See Chapter 2 and Appendix 2 for a more detailed discussion of this Recommendation.

- 1.33 Litigation has, so far, not served our patient groups well. We would not wish to remove the option to litigate, but for the future we propose a Redress Agency. This agency would supplement the current systems for resolution of disputes between patients and the healthcare system. This Redress Agency is not about addressing the needs of those already affected by the three interventions considered by this Review - these are addressed by **Recommendation 4**. It is about creating a new way of delivering redress in the future. There are precedents for this both in the UK and abroad, see Appendix 3.
- 1.34 The Redress Agency will provide a standing structure which is easy for patients to access and use. Rather than blaming individuals, decisions will be based on avoidable harm looking at systemic failings. This will encourage reporting by clinicians and so provide faster resolution for claimants. The Redress Agency will administer decisions using a non-adversarial process. The support or redress offered could be both financial and non-monetary.
- 1.35 To enable flexibility to adapt and respond to situations as they arise, different injury types would have separate schemes. Each scheme would have its own eligibility criteria and its own funding.¹⁴ A levy for pharmaceuticals could be paid into a pharmaceuticals scheme and separately a levy for medical devices could be paid into a medical devices scheme. Placing such products on the UK market should be made conditional upon contributing to a scheme. The Redress Agency would administer these schemes.
- 1.36 The costs of running the Redress Agency could be met by contributions from manufacturers and the state, but it must be situated outside the current organisations and the exercise of its functions must be entirely independent.
- 1.37 Those responsible for the Redress Agency will have an important role to play in harm prevention as adverse event reports would be centralised, so enabling data to be provided that will help regulators detect signals earlier.

Recommendation 3: A new independent Redress Agency for those harmed by medicines and medical devices should be created based on models operating effectively in other countries. The Redress Agency will administer decisions using a non-adversarial process with determinations based on avoidable harm looking at systemic failings, rather than blaming individuals.

¹⁴ Money for redress payments from schemes could come from various sources, including government, industry and litigation/out of court settlements. Different schemes would not cross subsidise.

- 1.38 In our view all three of the interventions have caused avoidable psychological harm in some patients. It is clear that mesh has caused significant physical harm and valproate has caused physical and neurodevelopmental harm. We believe that the state and manufacturers have an ethical responsibility to provide *ex gratia* payments¹⁵ to those who have experienced avoidable damage from the interventions we have reviewed. We recommend these schemes provide discretionary payments. Each of the three interventions should have its own scheme with tailored eligibility criteria. These payments¹⁶ are not intended to cover the costs of services which are available free of charge, such as health care and social security payments, but rather for other needs that could, for example, include travel to medical appointments, respite breaks or emergency payments where a parent has had to stop working to cover care. Patients have waited far too long for redress. Any scheme must be set up promptly. However, each should be structured so that it can be incorporated into the wider Redress Agency for the future as set out in **Recommendation 3**.
- 1.39 Individuals who obtain compensation from litigation or from out of court settlements (like J&J's Scottish pelvic mesh settlement) will not need recourse to these schemes.

Recommendation 4: Separate schemes should be set up for each intervention – HPTs, valproate and pelvic mesh – to meet the cost of providing additional care and support to those who have experienced avoidable harm and are eligible to claim.

- 1.40 We believe that those harmed are due not only an apology but better care and support through specialist centres: specialist centres for mesh, and separately specialist centres for those affected by medications taken during pregnancy. As well as meeting clinical needs, these centres should act as a one stop shop, able to signpost and refer patients to other services including educational, social and welfare. NHS England as the commissioner should collaborate with other government bodies which provide these services. As centres of excellence, such centres should have the responsibility to research better treatments and to audit outcomes. We have been in discussions with NHS England about commissioning these centres. At the time of writing, the commissioning process for specialist

¹⁵ *Ex gratia* payments, payments driven by a sense of moral obligation rather than a legal liability, have been provided for iatrogenic injuries; the vCJD fund, the vaccine damage payment unit and infected blood payments are three UK examples. In France the government pay into a fund for valproate damage, see <https://www.oniam.fr/valproate>

¹⁶ As per the Nordic patient and pharmaceutical injury compensation schemes, see Sonia Macleod and Christopher Hodges *Redress Schemes for Personal Injuries* (2017, Hart)

mesh centres is ongoing and we have been actively engaged in this process, see Chapter 5, paragraphs 5.12 – 5.13.

Recommendation 5: Networks of specialist centres should be set up to provide comprehensive treatment, care and advice for those affected by implanted mesh; and separately for those adversely affected by medications taken during pregnancy.

- 1.41 Post Brexit, the Medicines and Healthcare products Regulatory Agency (MHRA) will have to change, as indeed it recognises. This provides an opportunity to bring much needed cultural and legislative reform and to become more public-facing. The MHRA does not have the public profile of some other international regulators, such as the US Food and Drugs Administration (FDA). If they have concerns patients need to know what the MHRA does and how to contact it. The MHRA must work both for patients and with them. Reform, underpinned by legislation, is needed so that the views of patients are systematically listened to and their experiences of medications and devices are used to inform licensing and regulatory decisions. These strategic themes are further explored in Chapter 2 Theme 11.
- 1.42 For both medicines and medical devices there is a need for more robust, publicly accessible post-marketing surveillance. This should include mandatory requirements on healthcare organisations to report adverse events within a designated time period. The MHRA should provide assessments of the risks of individual medicines or devices and of classes of medicines or device where one or more members of the class carries an elevated risk.
- 1.43 The spontaneous reporting platform for medicines and devices, the Yellow Card system, needs reform. It needs to provide a user-friendly, accessible, transparent repository of adverse event reports. We recognise that the MHRA has previously tried to persuade other EU member states to be more open over adverse device reports. In our view openness and transparency should be a statutory requirement for adverse event reporting in the UK. The MHRA should be required to invite representatives of those who report adverse events (both patients and healthcare professionals) to be involved in evaluating and making decisions on specific safety concerns.
- 1.44 Medicines have to pass tests of quality, safety and efficacy before reaching the market. Medical devices are less rigorously examined before they are first marketed. This is because devices continually evolve, so by the time a clinical trial was complete the device may be onto a new iteration. Unlike medicines many implantable medical devices are intended to be permanent.

- 1.45 At present the MHRA has no involvement in the pre-market phase of medical device development. It should develop a proactive regulatory role for devices that is more akin to the licensing of medicines; this must be clinically focussed and at least as stringent as the new EU Medical Devices Regulations (MDR). The MHRA should keep a register of all devices approved for the UK market. Manufacturers should be required to apply to the MHRA before marketing their device. The MHRA should assess the application in a way that is proportionate to the risks posed taking into account relevant factors such as, the evidence base supplied, approvals in other jurisdictions, and the post-marketing surveillance plans. If approved a device will be added to the register. Marketing approval for devices should be a staged process, progressing to wider use and dissemination of the device as more information becomes available.¹⁷ In the event of an issue with a device the MHRA must have the power to remove a device from the register. Given there are an estimated 600,000 or more devices on the market we recognise that initially this will almost certainly involve some ‘grandfathering’¹⁸ of currently marketed devices.

Recommendation 6: The MHRA needs substantial revision, particularly in relation to adverse event reporting and medical device regulation. It needs to ensure that it engages more with patients and their outcomes. It needs to raise awareness of its public protection roles and to ensure that patients have an integral role in its work.

- 1.46 Post-market surveillance for devices and medicines needs to be high-quality and comprehensive, and it can be greatly facilitated by digital technology and big data. It became apparent to us that there were problems with obtaining comprehensive data and creating registries. We know that mature registries can deliver good-quality long-term outcome data using measures that matter to patients. They are, however, few and far between and all too often prompted by catastrophe.
- 1.47 We propose a two-stage process for data gathering. Firstly, the setting up of a mesh database with comprehensive coverage. In November 2019 the Secretary of State accepted what we had to say and mandated the requisite data collection by NHS Digital. The second stage will consist of establishing a mesh registry or registries to investigate specific issues in depth. Contact information can be extracted from a database into the registry to enable this research to take place.

¹⁷ ‘Evidence, Healthcare and Medical Devices & Implants’ Report from the Healthwatch Symposium 17th June 2019.

¹⁸ Grandfathering is when a medical device that was already on the market when an applicable law comes into force continues to be sold without restriction. Under the 1993 European Medical Device Directive, for example, some devices were exempt from meeting the new directive and allowed to continue being marketed.

- 1.48 Ultimately the goal must be to establish a database for all implantable medical devices, which can feed into registries as required.
- 1.49 While this recommendation focuses on medical devices, consideration should be given to the creation of comparable databases for specific medications, for example the use of medications during pregnancy.

Recommendation 7: A central patient-identifiable database should be created by collecting key details of the implantation of all devices at the time of the operation. This can then be linked to specifically created registers to research and audit the outcomes both in terms of the device safety and patient reported outcomes measures.

- 1.50 We have been concerned by conflicts of interest, both potential and real, in the provision of care or treatment, particularly where doctors have financial and other links with the pharmaceutical and medical device companies. Currently there is no central register of clinicians' financial and non-financial interests.
- 1.51 Other regulators should consider similar requirements as necessary, and the Professional Standards Authority should evaluate whether conflicts of interests have been adequately declared.
- 1.52 There is also no easily accessible means of identifying the accredited competencies of individual clinicians. The General Medical Council (GMC) has introduced registration for GPs and for specialists who want to practise as consultants. We recommend that this should be expanded to include all doctors' particular clinical interests (and any supporting accreditation).
- 1.53 We believe that responsibility for transparency of interests should not lie only with the medical profession. Medicines and medical device manufacturers should also ensure that they publish details of payments and payments in kind that they make to teaching hospitals, research institutions and individuals. This should be a statutory requirement similar to the Physician Payments Sunshine Act 2010 in the US. Consideration should be given as to where these disclosures should be published, including potentially expanding Disclosure UK¹⁹ and making it mandatory.

¹⁹ <https://www.abpi.org.uk/our-ethics/disclosure-uk/>

Recommendation 8: Transparency of payments made to clinicians needs to improve. The register of the General Medical Council (GMC) should be expanded to include a list of financial and non-pecuniary interests for all doctors, as well as doctors' particular clinical interests and their recognised and accredited specialisms. In addition, there should be mandatory reporting for pharmaceutical and medical device industries of payments made to teaching hospitals, research institutions and individual clinicians.

- 1.54 Our recommendations are designed to reduce the risk of similar cases of avoidable harm in future and to pave the way for a healthcare system that looks and feels very different from the past. It should not take years of campaigning by patients and yet another series of reviews or inquiries to achieve this.
- 1.55 We hope this Government, and all those bodies that comprise the healthcare system, will take heed of what we have to say, and that our recommendations, if accepted in full as we believe they should be, will be implemented with real determination and a sense of urgency. Our final recommendation shifts the focus to implementation.

Recommendation 9: The Government should immediately set up a task force to implement this Review's recommendations. Its first task should be to set out a timeline for their implementation.

Our Report

- 1.56 In the following chapters these Recommendations are supplemented by a series of 'Actions for Improvement'. Taken together and implemented, they are designed to better the patient experience, improve patient safety and help restore trust in the system. A complete list of our Recommendations and Actions for Improvement can be found in Chapter 8.

2 Overarching themes

- 2.1 In the chapters that follow we set out our findings for each of the three interventions we were asked to consider based on the evidence we received and a thorough analysis of our timeline of events. We look in detail at what happened in the past and we identify what we consider to be the missed opportunities when avoidable harm could have been prevented. Along the way we reflect on the improvements – clinical, managerial, regulatory and administrative – that had they been in place would have made a difference.
- 2.2 However, even a cursory reading of these chapters suggests a number of themes that span all three and which almost certainly resonate in other areas of medicine and for other interventions. We address these now and set out our ‘Actions for Improvement’ at the end of the chapter.

Theme 1: ‘No-one is listening’ – The patient voice dismissed

‘I have had a constant battle to get the help and treatment I needed with my mesh complications. ‘Gaslighting’²⁰ and a ‘fobbing off’ culture appears to be rife...’

A mesh-affected patient

- 2.3 In our travels around the country and in the volume of emails and correspondence we received, the personal written testimonies and video-recorded stories, patients – almost universally women – spoke in disbelief, sadness and anger about the manner in which they were treated by the clinicians they had reached out to for help. The words ‘defensive’, ‘dismissive’ and ‘arrogant’, cropped up with alarming frequency. They spoke of being ‘gaslighted’ and of not being believed, particularly in relation to pelvic mesh and the suffering of pain. Women, in reporting to us their extensive mesh complications, have spoken of excruciating chronic pain feeling like razors inside their body, damage to organs, the loss of mobility and sex life and depression and suicidal thoughts. Some clinicians’ reactions ranged from ‘it’s

²⁰ Gaslight (vb): To manipulate (a person) by psychological means into questioning his or her own sanity. Oxford English Dictionary. Etymology: title of George Cukor’s 1944 film ‘Gaslight’ (based on a play by Patrick Hamilton first performed in 1938) in which a man psychologically manipulates his wife into believing that she is going insane.

all in your head’ to ‘these are women’s issues’ or ‘it’s that time of life’ wherein anything and everything women suffer is perceived as a natural precursor to, part of, or a post-symptomatic phase of, the menopause. For the women concerned this was tantamount to a complete denial of their concerns and being written off by a system that was supposed to care.

- 2.4 The consequences of not being believed and not being listened to are far reaching. It immediately sets the tone for a patient-clinician consultation that is far from equal and precludes any form of shared decision-making around future care and treatment. The patient is vulnerable and feels unable to challenge and question. The patient is ignored and feels belittled.

‘the person I once was, she has gone and no-one seems able to help me. No-one is listening.’

A mesh-affected patient

‘If there was no reason for my symptoms I was just a wuss, not trying hard enough to get better, being soft... I could not at first contemplate getting an assessment and opening myself up to any further rejection by my medical colleagues, when they don’t listen you feel like a fraud... So, to my former medical colleagues I say this... I do accept for the majority of women this [mesh implant] is a successful procedure. I do however believe there is a huge unconscious negative bias among you all towards middle aged females in chronic pain. As more information is now coming out about the risks of mesh some of you are still choosing to downplay or actually disbelieve these facts...’

A former GP and mesh-affected patient

- 2.5 We make no apology for quoting at length from these testimonies nor from the oral evidence given to the Review by Ms Yvette Greenway (Mashed up by Mesh) and her partner, an eminent lawyer, on this specific point. It so clearly demonstrates why arrogance and dismissive attitudes – so entirely inappropriate for a health care professional – can have no place in the consulting room. Mr Michael Mansfield QC’s reputation and expertise in his own field is founded on his ability to ask difficult questions under pressure and forensically challenge evidence in a public court of law. Although he was not the patient, he told us in a later email *‘that I was so shocked and confounded by the dismissive assertions of a leading expert in the field that I did not take issue with them on the spot’*. This speaks volumes about some clinicians’ attitudes and the impact their attitudes can have on those who come to them seeking help. Surely it is time for the medical profession to sit up, listen and take stock.

Extract from ‘Mashed up by Mesh’ oral hearing testimony (21st November 2018)

Michael Mansfield: ... But this consultant, and there I was witnessing exactly what Yvette has described, is actually treating her as a – well, you know women they have these periods in their livesI couldn’t believe it. This was his assessment. Actually don’t worry about it, and he was ready for the next patient.

...If I treated someone like that, I would feel I was not discharging my obligations, I wasn’t in a caring profession.

Cyril Chantler: Did you point it out?

Michael Mansfield: I’ll be honest no we didn’t. I think we were both shocked, both got outside and went in the car, and we looked at each other and thought – ... what is this?

Michael Mansfield: ... I’m used to asking questions all the time. But actually I suddenly experienced what a lot of people tell me which is, you’re in the presence of an expert.

Michael Mansfield: You have to reflect, and so you’re mildly humble about it all and think well maybe he knows more than we do? Maybe there’s something we’re missing here. The full impact of the way he’s treated you doesn’t really impact itself at the time until moments later. Then you think, we’ve just been through what everybody talks about.

- 2.6 We know that women who accept a normalisation of their pain tend to seek the help they need far later than they should. This precludes the possibility of early, less invasive treatment with potentially better outcomes. It also takes its toll, physically, mentally and emotionally on the patient and their family and imposes ultimately a far greater cost on the NHS and the healthcare system to treat and attempt to put right.

‘Some parents have been accused of abuse because poorly educated clinicians have not recognised the complex symptoms that manifest as FACS [Fetal anti-convulsant syndrome]’.

Parent of a child affected by Foetal Valproate Spectrum Disorder

*'I know that the full harm done by sodium valproate is barely understood or even recognised by anyone other than the family that live it.'*²¹

Branwen Mann, Young People Affected by Sodium Valproate

*'They would tell you there is nothing wrong with you and that you are just a hysterical woman...'*²²

Teresa Hughes, Meshies United

*'I could guarantee you if you walked into any general practice in the UK and showed the GPs a piece of mesh very few of them would know immediately what it was. They have no idea. It's not because they don't want to know, it's because ... they don't work in that sphere.'*²³

Dennis Williams, retired GP, Welsh Mesh Survivors Group

- 2.7 Patients spoke of their frustration with GPs, usually their first port of call and gatekeeper to accessing secondary and specialist services. How little they seemed to understand about the symptoms being presented. This was as true for pelvic mesh sufferers as for the families of children suffering from Foetal Valproate Spectrum Disorder. Both groups described having to 'educate' their GPs in order to access the right diagnosis and the services they needed. Failure to do so could and did often mean a sense of abandonment by the system or being pushed from pillar to post because no-one was listening to, let alone hearing, what the patient had to say. Failure to get it right first time through ignorance and a general lack of awareness has only added to the stress felt by so many who contacted us. Patients should not have to fight for a proper diagnosis. They should not have to be the 'educators'. They should certainly not have to face accusations of abuse when seeking help. And they should not be left without the right support when things go wrong.

'It has rocked my faith in those in authority.'

'I've been fighting for answers my entire life. It's exhausting.'

Parents of children affected by foetal valproate spectrum disorder

²¹ OH Young People Affected by Sodium Valproate 20th November 2018.

²² OH Meshies United 21st November 2018.

²³ OH Welsh Mesh Survivors Support Group 21st November 2018.

- 2.8 Put simply, the system has not been listening as it should. When it has listened, it does not always know how to respond. It does not recognise its own failings in this regard. Not surprisingly those patients affected, their family and friends want answers. When they try to escalate their concerns, whether to the local Patients Advice and Liaison Service, to their Trust management teams or to the regulators, they have found these services unresponsive – either unable or unwilling to help. Patients have lost trust in those in positions of authority whether it be the medical profession or those responsible for delivering our healthcare services. The appointment of a Patient Safety Commissioner will provide a focus for patients; they will finally know that the patient voice will count when and where it matters.

Theme 2: 'I'll never forgive myself' – Parents living with guilt

- 2.9 We have been deeply saddened by the overwhelming sense of guilt we encountered on our travels - a guilt that has not lessened with the passage of time. We do not underestimate the additional psychological trauma this must bring with it.
- 2.10 Mothers are burdened by the guilt of having taken tablets during pregnancy. Mothers who took sodium valproate during pregnancy to manage their seizures without knowing the risks this could pose for their unborn children. Mothers whose guilt stems from a deeply-held conviction that their use of a hormone pregnancy test unwittingly damaged their child. We have heard at first hand the deep frustration, sorrow and dignified anger at the loss of lifetime opportunities brought about by the physical and developmental disabilities their children experienced. Parents, deeply anxious about what will happen to their adult child when they are no longer there for them. In the case of sodium valproate, affected mothers knowing that those same children in turn so often become their part time carers and at a relatively young age too, so adding to the burden of guilt.
- 2.11 The same burden of guilt is there for women affected by mesh. Risks they did not know about at the time they consented to their procedures; procedures they did not always need to have, given the degree of their incontinence or prolapse condition. The complications that followed have reduced so many to a shadow of their former selves, taking a terrible toll on partnerships and family life.
- 2.12 We know it is unlikely to absolve the guilt felt by any of these women but we repeat what we have said throughout the Review – *'it was not your fault.'*

Theme 3: 'I was never told' – the failure of informed consent

'I feel as though I am an unsuspecting, unwilling participant in a cruel experiment that has gone wrong. This is how many of us feel. What has happened to us cannot be allowed to happen ever again.'

'This rhetoric, "It is not the Mesh being talked about in the media" is still being used. And the fact that MESH is still being inserted in this way, without fully INFORMED consent... is disgusting and disheartening.'

Women affected by pelvic mesh implants

'Had I realised the full implications of this medication I would never have taken it.'

'Our daughter has been affected by me taking medication and we were given the wrong information... despite the facts being known and repeated requests for information... the result is devastating on us as a family.'

Women whose children were affected by sodium valproate exposure during pregnancy

'Why, I have asked myself a million times, did the doctor give me the drug? I already knew I was pregnant.'

'I didn't think anything about it at the time as I had no experience of anyone close to me being pregnant and I trusted that doctors would do the best for me.'

Women who took hormone pregnancy tests

- 2.13 Informed consent matters. It is the indispensable basis for the provision of healthcare and treatment by clinicians and it goes to the very heart of the patient-clinician relationship. The 2015 landmark case of *Montgomery v Lanarkshire Health Board* held that obtaining consent needs to be framed around what information an individual patient requires, and that this should always have been the case.²⁴
- 2.14 It is the patient's right to be told whatever information they need and in a manner that they understand – not what the reasonable clinician chooses to say – to make a decision on whether or not to proceed with a particular procedure or medication.

²⁴ *Montgomery v Lanarkshire Health Board* [2015] UKSC 11.

This means tailoring the consent conversation to the specific concerns of the individual patient, their attitude to risk, their understanding of the treatment options available and the potential adverse outcomes of those options both in the short and longer term. Where adverse outcomes are unknown, patients have an absolute right to know that too. They also have the right to know how any concerns about their healthcare treatment will be followed up. This, however, has not been the experience of so many who have given evidence to us across all three interventions.

- 2.15 We have been appalled by the numbers of women who have come forward to say they never knew they had had mesh inserted, or where they gave consent for ‘tape’ insertion they did not know they were being implanted with polypropylene mesh or were misinformed as to the extent of longer term adverse side effects. They did not know because no-one told them, let alone sought their properly documented informed consent. And we subsequently heard from women who underwent mesh removal surgery on the understanding that it would be a full removal. They consented to the operation on the basis of that understanding only to discover in the weeks, months, and in some cases years that followed that that was not the case.
- 2.16 We heard from women who were never told of the effect their medication for epilepsy could have on their unborn children or, if they had been alerted to the risk, they were reassured that those risks were low and could be scanned for and fixed. In the case of HPTs, women told us of going to their GPs to seek confirmation of their pregnancy and being offered a couple of sample pills from a desk drawer to be taken on two consecutive days. In many cases, there was no prescription, no discussion of risk, no mention of any suspected concerns about ingesting synthetic hormones in the early stages of pregnancy.
- 2.17 These are late 20th and early 21st century stories. No longer can informed patient consent be anything other than a true equality of partnership in the decision making process between patients and their treating physicians. Their care and treatment should not be a series of events that happened to them. Rather, every patient should be able to stand back, look at their patient journey and say ‘*I recognise my handwriting all over those choices.*’
- 2.18 In their evidence to the Review, the professional associations admit clinicians have not always ‘*done justice*’ to the process of acquiring informed consent.²⁵ The GMC’s position is that Montgomery brought the law up to date with their recommendations on good clinical practice. Ms Swati Jha, currently Chair of

²⁵ OH British Association of Urological Surgeons (BAUS), British Society of Urogynaecology (BSUG), Pelvic Floor Society (PFS) 7th February 2019.

the British Society of Urogynaecologists disagreed. She told us, *‘On the issue of informed consent ...We haven’t done as well as we should have done. The consent process did fall below a reasonable standard. I think Montgomery changed that.’*²⁶

Dr Aidan Fowler, National Director of Patient Safety at NHS England and NHS Improvement (NHSE&I) admitted: *‘I think there were issues around how consent was obtained. I think there was a tendency to say “I’ve got just the thing for you” in some cases and you will have heard that I’m sure. It is very difficult to change that sort of behaviour overnight because as you have seen it was more widespread than we might have hoped.’*²⁷

- 2.19 We agree with Ms Jha and Dr Fowler. Montgomery does represent a watershed, at least in principle. Changes in universal practice have been slower to catch up as we heard, and not only from patients. Witness this opinion voiced by a clinician in a debate at the 2019 annual conference of the International Continence Society in Gothenburg, *‘...we all counsel patients in a different way and we all counsel patients towards operations we prefer doing and think we are good at...’*²⁸
- 2.20 In response to Montgomery we have seen a rapid growth in the production of patient information leaflets that differ hugely in the amount of information on risks and benefits they present. The sheer variety of patient information leaflets available and the consent forms that flow from these are bewildering and a major source of confusion.
- 2.21 More thought needs to be given to help patients conceptualise risk. For example, talking about developmental delay or a six point deficit in IQ for a valproate-affected child may sound manageable but fails to convey the reality that the child might never grow up to live independently. **Information should be conveyed to patients in a way that is clear and meaningful. Talking to, or hearing from, others who have experienced the same intervention with or without complications – whether face to face, through Skype or from a video-recorded conversation – could be hugely beneficial and should be considered as part of the informed consent process.**
- 2.22 Patient decision aids (PDA) are important. If they are to be credible they must reflect the most up-to-date and valid clinical consensus of the risks and benefits associated with the intervention in question, including what is not known. PDAs should be validated, and standardised for each procedure. Most importantly, they must have been jointly developed with patients so that they accurately and fully

²⁶ *ibid.*

²⁷ OH NHS Improvement 26th March 2019.

²⁸ Clinician debate chaired by Professor Linda Cardozo at the International Continence Society Conference, Gothenburg, September 2019.

reflect the patient experience and outcomes. **We see no reason for there ever to be more than one collaboratively produced and agreed patient decision-making aid for each surgical procedure or medical intervention. We recognise that tailored versions may be required for different populations (for example if a procedure is carried out in an adolescent and adult population), but the core information related to risks, options and alternatives should remain the same. The National Institute for Health and Care Excellence (NICE) should lead in facilitating that clinical consensus.**

- 2.23 The GMC told us in evidence that in 2018 they received 120 complaints on the issue of patient consent. Of these, 84 were deemed either as requiring no further action before investigation or closed during investigation.²⁹ Given the extent and range of concerns we have heard on this same topic, this seems in our view a very small number in the context of over 260,000 doctors currently licensed to practise.
- 2.24 The GMC are preparing new guidance on decision making and informed patient consent. We expect this to set out as good clinical practice that **every patient-clinician consultation around consent should be both proportionate to the circumstances and appropriately documented. Both the patient and clinician's discussion, comments and concerns should be noted. Today's mobile technology makes it easy for every planned conversation about patient consent to be audio or video recorded by the patient (with the agreement of both parties). This allows the patient to take away and reflect upon the conversation, which benefits both patients and clinicians. In future this record should also be stored with the patient's electronic health record.**

Theme 4: Redress – 'We want justice'

'...we want justice, it's like we are the forgotten ones.'

Mesh-injured woman

Past harms

- 2.25 The suffering we have seen has arisen as a result of medications or devices provided by a doctor. NHS and social care systems are designed to ensure that care and support are provided for affected individuals. However, we have heard from individuals where the support offered has fallen short of what is needed. Across

²⁹ OH General Medical Council (GMC) 14th March 2019, and written evidence from the GMC.

all three of our interventions we have heard of failures of health and social care services to interact around the individual.

The struggle to obtain appropriate social care and benefits

*'There's no cure for FAS so what we would like is access to speedy PIP claims, avoiding the red tape for children affected.'*³⁰

Jo Cozens, Organisation for Anti-Convulsant Syndrome (OACS)

- 2.26 We have heard from individuals who have described how they have struggled to access the benefits that they are entitled to. As part of our Review we have engaged with the Department for Work and Pensions (DWP) in order to get a better understanding of their eligibility assessment processes.
- 2.27 Benefits assessments are not straightforward and can be daunting and hugely stressful for individuals with complex issues. When we met with senior officials at DWP we explored with them what could be done to make the benefits assessment process for Personal Independence Payments (PIP) less stressful. We have proposed to DWP that the patient groups contribute directly to a new insight condition report for each of these interventions that would help paint the picture of daily living with these conditions. DWP have commenced that process.
- 2.28 **There is a need for additional training for those carrying out assessments for DWP based on the insight condition reports. This should help those carrying out the assessments to make equitable decisions.**

Education

- 2.29 Children affected by sodium valproate and their parents can face an additional hurdle, the education system. Children with FVSD may have a range of neurodevelopmental effects, including intellectual disability, difficulties with language and memory, learning and behaviour problems. However, a lack of awareness among health, social care and educational providers often delays access to diagnosis and referrals to support services, including ensuring an appropriate Education, Health and Care Plan is in place (see Chapter 4).

³⁰ OH OACS and OACS Ireland 20th November 2018.

Access to medical treatments

‘...our focus is also ensuring that the thousands of mesh-injured women across the country are given the medical help, treatment and support to allow them to live their lives as best they can after the catastrophic outcomes they have suffered...’³¹

Scottish Mesh Survivors

- 2.30 An overarching theme too has been a loss of trust in the medical profession and an inability to access appropriately skilled and trustworthy specialist services. We have heard from mesh-injured women who have so lost trust in the NHS provision for mesh removal that they have been prepared to pay for expensive private surgery, and in some cases have travelled overseas at great cost, both personal and financial. Across all three interventions we have consistently heard from those who have been unable to find doctors to address their needs.

Specialist centres

- 2.31 We therefore recommend the creation of two different types of specialist centres, (**Chapter 1, Recommendation 5**).
- a. Centres for those with congenital anomalies believed to be due to in utero medicine exposure.
 - b. Specialist mesh centres where there is expertise in how to treat mesh complications and in the most appropriate techniques for mesh removals.

Discretionary Schemes for those harmed by HPTs, valproate and pelvic mesh

- 2.32 We are precluded from considering individual compensation, but we have considered redress more widely. In our view, litigation has not proved useful to the majority of the affected individuals we have heard from.³² We are aware of a handful of successful claims for valproate and mesh against individual doctors, but to date we are not aware of any successful product liability cases against manufacturers of HPTs, valproate or pelvic mesh products in England and Wales.
- 2.33 We have seen the avoidable harm suffered and we feel there is a strong ethical responsibility to provide redress. There are examples of situations where the

³¹ OH Scottish Mesh Survivors 21st November 2018

³² The proposed Directive on representative actions may change the litigation landscape in the EU towards a more favourable position for mass claims, but any implications for the UK are uncertain <https://data.consilium.europa.eu/doc/document/ST-14600-2019-INIT/en/pdf>

government makes *ex gratia* financial contribution for injuries caused by medicines or medical treatments without any admission of liability, for example infected blood payments, variant Creutzfeldt-Jakob Disease (vCJD) Trust and vaccine damage payments. In France the government pays into a fund for valproate damage.³³

We consider discretionary schemes for HPTs, valproate and pelvic mesh should be set up. These three schemes should provide discretionary payments for the costs of additional needs caused by the avoidable harm we have been told about (Chapter 1, Recommendation 4).

- 2.34 Each of the three interventions should have tailored eligibility criteria. Payments from these schemes should be discretionary and based on avoidable harm. These payments should be similar to those given in the Scandinavian patient and pharmaceutical injury redress schemes.³⁴ This means they are not intended to cover the costs of services which are available free of charge, such as health care and social security payments, but are to cover additional needs, to include for example travelling to treatment, respite breaks and stopgap payments where someone has to stop working to provide care for an affected individual.
- 2.35 Care should be taken to explore the implications of any payments from these three funds on any benefits payments received by the affected individual and their family members. Consideration will need to be given to the interactions between payments from these schemes and the benefits and taxation systems. Should an individual obtain compensation for their injuries through litigation then any corresponding payments that the scheme had made to that individual would need to be taken into account.
- 2.36 Patients have waited far too long for redress, these schemes must be set up promptly. However, they should be structured so that they can be incorporated into a wider Redress Agency.

A Redress Agency and schemes for future harm due to medicines and medical devices

- 2.37 The majority of inquiries or reviews such as ours look at a single issue, and any redress they recommend will be focussed around that one issue. Our Review is unusual in covering three very different interventions, and this has given us a wider and more systemic approach to redress. **For the future, we have recommended a Redress Agency should be set up on an avoidable harm basis which looks to systematic failings, rather than blaming individuals. This encourages reporting and should provide faster resolution for claimants (Chapter 1, Recommendation 3).**

³³ <https://www.oniam.fr/valproate>

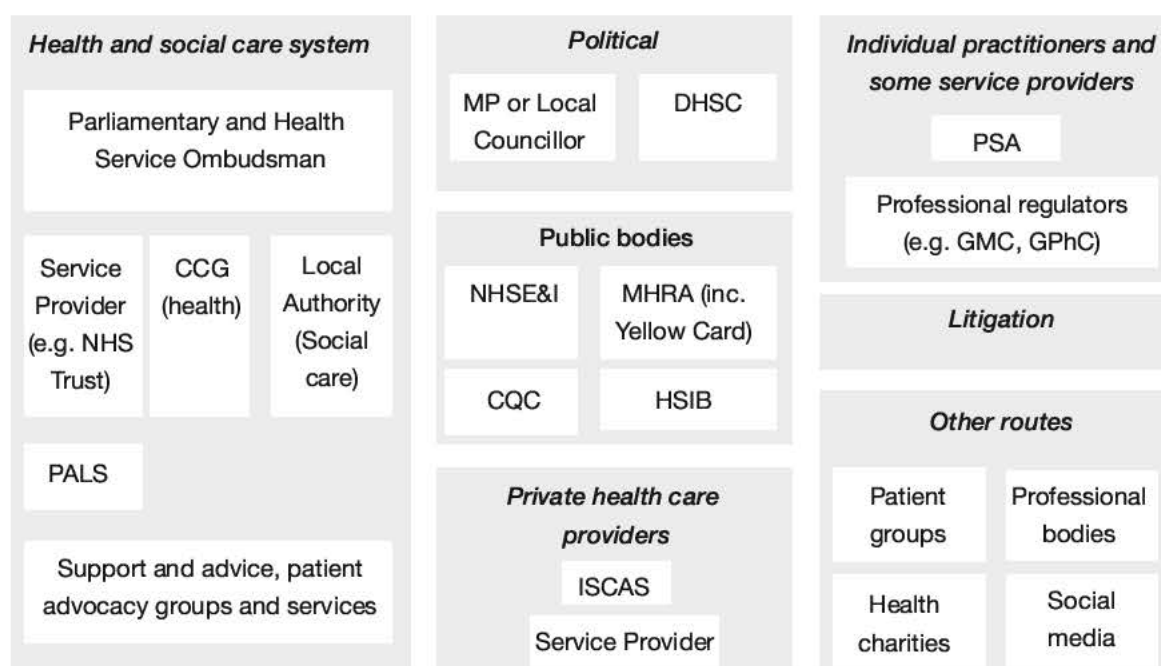
³⁴ Macleod, S and Hodges, C 'Redress Schemes for Personal Injuries' Hart 2017.

- 2.38 The Redress Agency would provide a standing structure to administer decisions using a non-adversarial process. This model is simple for patients to access as there is one point of contact. This structure enables flexibility to adapt and respond to situations as they arise.
- 2.39 The Redress Agency will have an important role to play in harm prevention as claims for adverse events would be centralised, enabling data to be provided that will help regulators detect signals earlier.

Theme 5: 'We do not know who to complain to' – Complaints

'Should sick patients have to go through complaint after complaint to get help?'

Mesh-injured patient



CCG (Clinical Commissioning Group); CQC (Care Quality Commission); DHSC (Department of Health and Social Care); GMC (General Medical Council); GPhC (General Pharmaceutical Council); HSIB (Healthcare Safety Investigation Branch); ISCAS (Independent Sector Complaints Adjudication Service); MHRA (Medicines and Healthcare products Regulatory Agency); NHSE&I (NHS England and NHS Improvement); PALS (Patient Advice and Liaison Service); PSA (Professional Standards Authority)

Figure 2.1 Routes for making complaints in England

- 2.40 Many of those affected by the interventions under review have expressed their frustration at the lack of a clear pathway for them to make a complaint or raise concerns about aspects of their care. A simple mapping exercise (figure 2.1) suggests a number of organisations that patients might interact with in order to make a complaint. All have limitations in remit and outcome, some may be able to refer the complaint on to the appropriate organisation, others may signpost the patient on to another organisation to make another complaint.
- 2.41 Patients struggle to navigate the complaints system and it may take some time to find the correct organisation to complain to. All the while patients are still living with the complications that led to the original complaint, and may have had further upsetting experiences including surgeons dismissing their pain and other complications – patients described being ‘broken’ by this journey. For example, the GMC can only take complaints which relate to a doctor’s fitness to practise. However, two thirds of the complaints they received in the previous five years were not about a doctor; these included complaints about other professions, parking disputes, and other non-clinical matters.³⁵
- 2.42 We have frequently heard in both our patient engagement events, and in direct communication from those affected that this Review has been the first time they felt able to tell their story to someone who would listen. This is unacceptable. **Patients across the NHS and private sector must have a clear, well-publicised route to raise their concerns about aspects of their experiences in the healthcare system. It will be for the implementation task force (see Chapter 1, Recommendation 9) to address this problem.**
- 2.43 Investigations into clinical matters by the GMC are limited to the (most recent) event taking place within five years of the allegation, unless it is in the public interest. The GMC told us: *‘We interpret public interest quite low. So if it’s serious harm that’s been done and the patient has struggled around the system, then we will look at that.’*³⁶ However, prior to 1 January 2016, in addition to the public interest test, there had to be exceptional circumstances related to the particular case before the GMC would proceed to investigate. Patients have raised concerns that where there is a pattern of complaints relating to an individual doctor that spans years, these restrictions mean older complaints are not investigated by the GMC. This is a particular issue for interventions, such as those we have reviewed, where there may be a long delay between treatment and becoming aware of adverse events. **In our view, the time bar that limits GMC investigations into allegations of events that are over five years old should never get in the way of**

³⁵ OH GMC 14th March 2019.

³⁶ *ibid.*

establishing the evidence for a pattern of poor practice by any one clinician on the register. The GMC have told us they recognise this is an issue of public concern and they support proposals to *‘amend this rule as part of a package of changes to make (their) processes quicker and more efficient’*.³⁷ Any move to do so, however, would only be considered following a full public consultation.

- 2.44 Dissatisfaction with how the system has responded to complaints, sometimes multiple, about named clinicians and individual Trusts has been a common thread throughout our engagement with those affected. If complainants feel their complaints are being disregarded unfairly they, and others, will be discouraged from reporting their concerns and the system’s culture of denial and resistance to acknowledging mistakes will continue unchallenged. **The bodies that have received these complaints, including the GMC, the Care Quality Commission (CQC) and the individual Trusts should reassess what they have been told and satisfy themselves that they have taken necessary steps to identify any patterns and trends. They should inform the relevant organisations and Patient Safety Commissioner of outcomes of concern.** This will enable a system-wide reflection of these cases.
- 2.45 Complaints do not appear to be a priority; the NHS-wide Complaints Standards Framework for complaint handlers has been under development for years. The GMC again suggest that a lot of the complaints they receive are from patients who ‘haven’t got anywhere in the system’. They suggest that every Trust should make a senior board member responsible for complaints and complaint handling within their Trust, to ensure that these issues are considered at board level and any emerging patterns or themes addressed at that level. We believe this should go wider than Trusts. **All organisations who take complaints from the public should designate a non-executive member of the board to oversee the complaint - handling processes and outcomes, and ensure that appropriate action is taken.** All such organisations must also have a mechanism to feed into alerts of emerging issues and learning on an organisational, local and national level. A network of these nominated board members with oversight of complaints should help facilitate better and earlier signal detection across the healthcare system.

Theme 6: Duty of Candour – ‘preventing future errors’

- 2.46 It has long been accepted that if you want to build a safer healthcare system then errors need to be acknowledged and learned from.³⁸ Our Review covers a long time period, from 1950 onwards, and attitudes towards admitting mistakes and

³⁷ GMC written evidence to the Review.

³⁸ ‘To Err is Human: Building a safer healthcare system’ Institute of Medicine 1999.

apologising have improved in that time. However, there is still scope for further improvement. Many patients we heard from felt that clinicians have been reluctant to admit to any mistakes made during, or acknowledge any adverse outcomes from, an intervention. This lack of open conversation when things have gone wrong has contributed to a wider failure to recognise and raise concerns about the adverse effects of interventions.

- 2.47 Doctors have long had an individual professional duty of candour to be open and honest with patients if things go wrong, and this was reinforced with a joint statement from regulators of healthcare professionals in 2019.³⁹ Health and social care professionals also have a contractual duty of candor in their employment contracts. Unfortunately, these duties were not always adhered to, and a statutory Duty of Candour for NHS bodies was introduced in November 2014,⁴⁰ and expanded to all CQC-registered care providers in April 2015.
- 2.48 Failure to comply with this duty is a criminal offence, and CQC can take enforcement actions over any breach of the duty of candour. However, the Professional Standards Authority (PSA) report that the regulators are not identifying duty of candour breaches or considering them as part of fitness to practise panels.⁴¹ The statutory Duty of Candour has not been entirely effective.⁴²
- 2.49 Barriers to disclosure in the health and care system are well recognised.⁴³ NHS Resolution told us their perception was that *‘there has been a move away from a blame culture towards a more open culture in the NHS, where mistakes are more readily admitted, reported and discussed without fear of reprisal.’*⁴⁴ Despite efforts to facilitate the raising of concerns by healthcare professionals, such as the introduction of local Freedom to Speak Up Guardians,⁴⁵ we heard about a persistent culture of reluctance to speak out: *‘There is an inherent conflict in the NHS now, as somebody who works in it – there’s not an open forum for mistakes*

³⁹ Joint statement on the professional duty of candour https://www.pharmacyregulation.org/sites/default/files/joint_statement_on_the_professional_duty_of_candour.pdf

⁴⁰ Health and Social Care Act 2008 (Regulated Activities).

⁴¹ OH Professional Standards Authority (PSA) 10th January 2019.

⁴² Under Regulation 20 of the 2008 the Statutory Duty of Candour (DoC) applies to a notifiable safety incident. Notifiable safety incidents are those resulting in death, serious harm or moderate harm. We understand that since the statutory DoC was introduced reports in the National Learning and Reporting System of deaths and serious harms have remained fairly constant. Reports into NRLS of moderate harm have in fact dropped. It appears that the statutory DoC has not had the desired effect of increasing reporting and disclosure.

⁴³ For example see the 2013 report by the PSA *‘Candour, disclosure and openness: Learning from academic research to support advice to the Secretary of State’* and the 2015 *Freedom to Speak Up Review*

⁴⁴ NHS Resolution written evidence to the Review.

⁴⁵ Created in response to recommendations made in the Francis report ‘The Freedom to Speak Up’ (2015), the Freedom to Speak Up Guardians are appointed by an organisation to support workers to speak up when they feel that they are unable to do so by other routes.

*or errors or things going wrong. There's too much blame for individual clinicians and surgeons.'*⁴⁶

- 2.50 We believe that barriers to being open and honest must be minimised. We share concerns with others that litigation, which is blame-based and focusses on the actions of individual doctors, inhibits disclosure. It has been known for decades that the majority of mistakes are system errors, yet litigation deals with the culpability of individuals. Over twenty years ago in 'To Err is Human' the Institute of Medicine wrote, *'The focus must shift from blaming individuals for past errors to a focus on preventing future errors by designing safety into the system. This does not mean that individuals can be careless. People must still be vigilant and held responsible for their actions. But when an error occurs, blaming an individual does little to make the system safer and prevent someone else from committing the same error.'*⁴⁷
- 2.51 We endorse this approach. We believe that a cultural shift away from blame is needed to create a healthcare system where people are open and honest. We outline how we feel a no-blame, systems-based approach to delivering redress as a substitute for litigation could drive this shift in paragraphs 2.37 – 2.39 (see also Appendix 3). We believe this shift is essential to deliver a safer NHS where healthcare professionals have no reason to fear being candid and telling the truth to their patients. Whilst we support the new emphasis on supporting whistle-blowing we are not convinced that this in itself will solve this problem.

Theme 7: Conflicts of interest – 'we deserve to know'

*'As patients, we allow the medical profession access to our bodies, our thoughts and our lifestyles. All manner of information to better assist them in reaching decisions about the best course of treatment for us. We, the patients deserve the same, we should be aware of clinicians' allegiances or involvements whether they be financial or other. So we too can reach informed decisions about who is best to treat us, and how they should treat us.'*⁴⁸

Yvette Greenway, Mashed up by Mesh

- 2.52 The Review has heard concerns about the potential conflicts that arise as part of the financial links between drugs and medical device companies and consultants, hospitals or other organisations. We are also concerned about those that arose as

⁴⁶ OH Professor Carl Heneghan 27th November 2018.

⁴⁷ 'To Err is Human: Building a safer healthcare system' Institute of Medicine 1999.

⁴⁸ OH Mashed up by Mesh 21st November 2018.

part of the personal and professional interests of clinicians (in the past, present and future). This concern is not limited to the interventions under review, or to this country. Nor is this a new concern; a paper by the Institute of Medicine in 2009 raised significant risks that individual and institutional conflicts of interests were unduly influencing professional judgements, and that such conflicts *‘threaten the integrity of scientific investigations, the objectivity of medical education, the quality of patient care’* and may also *‘jeopardize public trust in medicine’*.⁴⁹

Clinician interests

‘I think it’s important that if I’m treating you, you know who’s paying me.’⁵⁰

Professor Carl Heneghan

- 2.53 The healthcare system is reliant on people motivated by the best outcomes for their patients. We recognise that they would not believe themselves to be swayed by any commercial, or other, influences. However, patients’ *perceptions* of conflicts of interests do not always mirror those of clinicians. We have heard particular concerns that clinicians have been paid or otherwise incentivised by manufacturers. This may influence their practice, and the course of action they recommend to patients, such as preferentially using particular procedures or drugs.⁵¹ We have also heard from women affected by mesh that their doctors have told them they can only provide the requested care in their private practice.
- 2.54 We asked the professional bodies and regulators about how the management of clinician interests and possible conflicts are addressed by their organisations. We were told about professional and voluntary arrangements, including publicly accessible voluntary registers for doctors,⁵² and for health professionals, organisations and pharma companies.⁵³ However, there is no centrally mandated register for healthcare professionals.
- 2.55 During our oral hearings, a number of professional bodies agreed with the idea of a national mandatory register of interests for doctors.⁵⁴ They, and others, recognised

⁴⁹ Lo, B and Field, MJ (Eds) ‘Conflict of interest in medical research, education, and practice’ Institute of Medicine of the National Academies Committee on Conflict of Interest in Medical Research, Education, and Practice. National Academies Press 2009 (p2) <http://dx.crossref.org/10.17226/12598>

⁵⁰ OH Professor Carl Heneghan 27th November 2018.

⁵¹ For example, see OH Sling the Mesh 21st May 2019; OH Professor Carl Heneghan 27th November 2018.

⁵² <http://www.whopaysthisdoctor.org/doctors>

⁵³ Disclosure UK, led by the ABPI <https://search.disclosureuk.org.uk/>

⁵⁴ OH BSUG/PFS 16th April 2019; OH Royal College of Obstetricians and Gynaecologists (RCOG); OH GMC/General Pharmaceutical Council (GPhC) 10th January 2019.

that patients and the public were not satisfied with the lack of detail in voluntary declarations, but raised a number of concerns about how declarations could best be used to ensure transparency of decision making. In their oral evidence to us the GMC said they fully support the idea in principle of enhancing the List of Registered Medical Practitioners to record clinicians' interests.⁵⁵ However, without legislative power, clarity about where responsibility lies, and support of the profession, they did not feel any major changes could be introduced.⁵⁶

- 2.56 All healthcare professionals should be open about their interests, and the professional regulators should consider how they can encourage disclosure. **We believe that the GMC should expand the List of Registered Medical Practitioners to include financial and non-pecuniary interests. The Department of Health and Social Care (DHSC) should address any legislative barriers to these changes. (Chapter 1, Recommendation 8)**
- 2.57 The GMC are concerned that *'there is lack of consistent and reliable data on what doctors are doing'*⁵⁷. We also heard from the Royal College of Obstetricians and Gynaecologists (RCOG) that the same procedure may be carried out by both accredited sub-specialists and by those who have done general training and developed an interest in specific interventions who, necessarily, will not have the same level of skill.⁵⁸ We believe that patients should be able to access information about the competencies of individual clinicians to make decisions about their care.
- 2.58 The GMC have introduced registration for GPs who wish to practise as a GP in the UK health services, and for specialists who want to practise as consultants. We are aware that they are working to introduce a framework for GMC-regulated credentials for doctors, which will be focussed on areas of practice considered to be high risk.⁵⁹ **We recommend that the information on the register should be made more comprehensive by expanding to include all doctors' particular clinical interests and any supporting accreditation (Chapter 1, Recommendation 8). Many hospitals in both the NHS and independent sector record consultants' special clinical interests on their own websites. As such they are subject to review through the appraisal process. This does not, however, bring those interests together in one central place.**

⁵⁵ OH General Medical Council (GMC) 14th March 2019.

⁵⁶ GMC. Developing the UK medical register. https://www.gmc-uk.org/-/media/documents/M06_Developing_the_UK_medical_register.pdf_69417294.pdf

⁵⁷ GMC written evidence to the Review.

⁵⁸ OH RCOG 7th Feb 2019.

⁵⁹ The GMC informed us of this in the Oral Hearing, this project has progressed. Information can be found on their website: <https://www.gmc-uk.org/education/standards-guidance-and-curricula/projects/credentialing>

Funding of organisations

‘MHRA has been too close to the industry... underpinned by common policy objectives, agreed processes, frequent contact, consultation and interchange of staff...[we] have little faith in the ability of medical institutions that are responsible for patient safety to be open and transparent over patient safety failings.’

Sling the Mesh, written evidence to the Review

- 2.59 A major concern raised by patient groups is the role of industry funding in organisations responsible for advice and regulation. The activities of the MHRA are currently funded primarily through the pharmaceutical industry on the medicines side, and 95% through the DHSC on devices. Additional funds for clinical trials and inspections of notified bodies come mostly from the DHSC. The MHRA told us that they ensured independence through stringent conflict of interest policies, and use of external experts without interests.
- 2.60 There are concerns about the movement of individuals between regulators and industry. Approximately 11% of staff in the medical devices division of the MHRA were previously employed in industry.⁶⁰ The MHRA emphasised the importance of the expertise of these employees. The approach taken is to manage conflicts, rather than to exclude them completely.⁶¹ People who come from industry cannot work on that company’s products or related products for a period ranging from two years to indefinitely. In addition, MHRA staff are not allowed to hold shares or have financial interests in the pharma or device industries. We recognise the importance of this expertise in the work of the MHRA. However, even if this approach is fully upheld, it leaves the MHRA open to both perceived and actual influences from industry. We note that of those working in the medical devices division of the MHRA who previously worked in industry, many are in decision-making roles.⁶² We believe that as part of the overhaul of the culture in the MHRA steps should be taken to ensure that the patient perspective and the public interest always takes precedence over the interests of industry, see Theme 11.
- 2.61 Across the three interventions we have come across conflicts of interest in the selection of experts to form part of expert working groups, advisory committees or to agree guidelines. An ideal expert would be an individual who is knowledgeable and respected in their field, but who has no personal, professional or financial links

⁶⁰ MHRA written evidence to the Review.

⁶¹ The MHRA policy for handling conflicts of interest can be found here: <https://www.gov.uk/government/publications/mhra-policy-for-handling-conflicts-of-interest>

⁶² MHRA written evidence to the review: Grades AO/EO (0); HEO/SEO (5); G7/6 (5); SCS1/2 (2).

which might influence their position. We recognise that it may not be possible, or even desirable, for an expert to have no interest in a matter being reviewed.

- 2.62 An inquiry into the review of transvaginal mesh implants in Scotland in 2017 found a number of conflicts of interest in those who took part in the review, including: clinical members being paid by pharmaceutical companies; members being involved in litigation; and one surgeon who had operated on one of the other members.⁶³ Similarly, the Chair of the patient group Association for Children Damaged by Hormone Pregnancy Tests (ACDHPT) raised concerns about conflicts of interest of members of the Expert Working Group (EWG) on Hormone Pregnancy Tests (see Chapter 3, paragraph 3.102).
- 2.63 We raised this issue with the MHRA at the oral hearing. They suggested the best approach was to rely on self-declaration and honesty, and to undertake action if things came to light, rather than investigation of each individual before they were accepted into the group.⁶⁴
- 2.64 These examples suggest that the system of self-declaration has not been sufficient. **Organisations should ensure clear governance arrangements to cover the potential conflicts of interests of any individual who participates in either regulatory activities or inquiries, including the composition of expert panels. Whilst it is to be expected that those people asked to participate should declare any potential conflicts of interest, the organisation should consider what is proportionate and whether it is appropriate to proactively check potential members' interests prior to their appointment.**

Manufacturers

'...you're more likely to get things sharpened up through the industry side than being reliant on the clinicians'.⁶⁵

Andy Williams, Pelvic Floor Society

- 2.65 We do not believe that responsibility for transparency of interests should fall only on the medical profession. Manufacturers should also take responsibility to ensure

⁶³ Bryan, C 'Scottish mesh review had serious failings' BMJ 2018; 363 :k4562; *An Investigative Review into the process of establishing, managing and supporting Independent Reviews in Scotland* (October 2018) available at: <https://www.gov.scot/binaries/content/documents/govscot/publications/independent-report/2018/10/investigative-review-process-establishing-managing-supporting-independent-reviews-scotland/documents/00542453-pdf/00542453-pdf/govscot%3Adocument/00542453.pdf>

⁶⁴ OH MHRA 27th February 2019 Session 1 / OH ACDHPT 14th February 2019 / MHRA Right of Reply attached to OH 14th February 2019.

⁶⁵ OH BSUG/PFS 16th April 2019.

that they publish details of payments they make to teaching hospitals and research institutions. At the moment there are voluntary arrangements in place between the Association of the British Pharmaceutical Industry (ABPI) and the Association of British Health Tech Industries (ABHI) and their respective manufacturers to ensure that individual clinicians are only paid through recognised research grants.⁶⁶

Voluntary declaration does not always work.⁶⁷ Patient groups and others have suggested that the UK put in place an equivalent to the American Physician Sunshine Payment Act, which places a statutory responsibility on medical product manufacturers to declare any payments or other transfers of value (including expenses) made to physicians or teaching hospitals. We agree. (Chapter 1, Recommendation 8)

Research

- 2.66 Clinicians have told us about the difficulty in securing research funding from established research bodies such as the National Institute for Health Research (NIHR).⁶⁸ Given the limited opportunities from these bodies, industry represents an important stream of funding. However, there is evidence that industry sponsored studies tend to find more favourable outcomes for sponsors' products.⁶⁹ Reviewers' rating of manuscript quality does not appear to be affected by disclosure of conflicts of interests.⁷⁰
- 2.67 The role of drug and medical device manufacturers in provision of financial support for research must be well managed to ensure evidence is trustworthy. Those who conduct, publish and use research should satisfy themselves that appropriate governance processes have been adhered to. **All journals should provide assurances to their readers that their Code of Practice relating to Conflict of Interest is compliant with the policy set out by the World Association of Medical Editors,**⁷¹ and has been scrupulously adhered to before they publish articles, particularly those which have been sponsored by third parties. This is particularly relevant to NICE and the MHRA who rely on this data to inform their decision making.

⁶⁶ ABPI Code of Practice: <https://www.abpi.org.uk/publications/code-of-practice-for-the-pharmaceutical-industry-2019/>

⁶⁷ For a discussion of this and other related issues, see Gornall, J. Vaginal mesh implants: putting the relations between UK doctors and industry in plain sight. *BMJ* 2018; 363:k4164 doi: [10.1136/bmj.k4164](https://doi.org/10.1136/bmj.k4164)

⁶⁸ Personal communications.

⁶⁹ Moynihan, R et al. 'Pathways to independence: towards producing and using trustworthy evidence' *BMJ* 2019; 367 :l6576 <https://doi.org/10.1136/bmj.l6576>

⁷⁰ John, LK et al. 'Effect of revealing authors' conflicts of interests in peer review: randomized controlled trial' *BMJ* 2019; 367 :l5896 <https://doi.org/10.1136/bmj.l5896>

⁷¹ World Association of Medical Editors policy on 'Conflict of Interest in Peer-Reviewed Medical Journals' <http://wame.org/conflict-of-interest-in-peer-reviewed-medical-journals>

Theme 8: 'Holding to account' – Guidelines and Quality

Guidelines

- 2.68 Across all three of the interventions we have seen the impact of a failure to implement available information and guidance. Here are just three examples, but the list is long:
- Hormone pregnancy tests continued to be used after the indication was removed
 - Patients not being offered conservative management options for stress urinary incontinence
 - Valproate being used as a first-line treatment, rather than for those intolerant of, or resistant to, other treatment
- 2.69 Guidelines are advisory, and are subject to interpretation and, rightly, dependent on the judgment of the clinician and the patient on what is best for that individual or in that circumstance. This does not absolve the healthcare system from a responsibility to monitor the uptake of guidance, ensure common practice is in line with recommendations, and take necessary actions for enforcement. **Annual appraisal is a contractual requirement for all NHS consultant and non-consultant career grade doctors. This should include providing evidence of awareness of relevant guidance in the doctor's area of practice. Additionally, if colleagues both junior and senior, are aware of failure to follow guidance which is detrimental to patient safety, they should report this. This should apply in the private or independent health sector as well as the NHS.**
- 2.70 Failure to be aware of or to follow guidance appropriately is not just a matter for the employing authority as it may call into question a doctor's fitness to practise. The GMC told us that even if a doctor doesn't always follow guidance this may not meet the threshold for action, such as referral to the GMC Fitness to Practise process.⁷² We accept that this is in line with the need to allow clinicians to agree the best course of action with each individual patient, but would **expect the system to be alert to and act if any doctor's practice causes concern in this respect**. Failure to act was indeed an issue noted by the Paterson Inquiry.
- 2.71 Others also have a responsibility to detect poor clinical practice. **Hospitals should encourage clinical audit and should have robust systems for monitoring quality**

⁷² OH GMC/GPhC 10th January 2019. In their written evidence to the Review, the GMC informed us that the most common reason for referrals to the GMC relates to 'knowledge and experience', which includes substandard treatment, suitable action not being taken, or inappropriate or irresponsible prescribing.

at Board level. The CQC should also assure itself that hospitals, both in the NHS and in the private sector, have robust quality assurance programmes, including following appropriate guidance.

- 2.72 In 2003 NICE issued guidance on the use of Tension-free Vaginal Tape (TVT) for Stress Urinary Incontinence (SUI). Neither NICE, nor any other body in the healthcare system, had the responsibility to monitor implementation or take action. At this time, the Commission for Health Improvement, and subsequently the Healthcare Commission strongly reinforced these core standards through inspection. There is no requirement on the CQC, as successor to the Commission for Health Improvement, to ensure compliance with NICE's interventional procedure guidance.⁷³ We are aware that the CQC have worked with NICE to develop a process to monitor key concerns around implementation of guidance during the inspection process. The CQC recognised the limitations of inspections – *'it is a snapshot when we go in, at that particular moment in time.'*⁷⁴ They have proposed organisations appoint an executive responsible for ensuring NICE guidance is being followed. Again, this should be part of the Board's quality assurance responsibility.
- 2.73 We also heard from the regulators about how they incorporate new concerns into their inspections. For example, in response to valproate and the Pregnancy Prevention Programme (PPP), the CQC initially asked how GP practices react to safety alerts, and as a consequence, have now refined their process to examine records to check alerts have been acted upon. Inspectors now ask about valproate on every inspection.⁷⁵ The General Pharmaceutical Council (GPhC) also raised with us the use of inspections to raise awareness of and improve compliance with the PPP in pharmacies.⁷⁶
- 2.74 NICE and the NHS in all four nations of the UK have agreed and documented the responsibilities of NHS organisations on safely introducing new procedures into practice.⁷⁷ The importance of this document has been highlighted by NHS Improvement in England.⁷⁸ NICE made further recommendations on how the system could encourage adherence to advice, including oversight by the regulator to provide assurance that health care providers have appropriate governance structures in place to ensure adoption of the new guidance. We agree with these recommendations, and would add that **those responsible for introducing new**

⁷³ NICE written evidence to the Review.

⁷⁴ OH CQC 26th March 2019.

⁷⁵ OH CQC 26th March 2019.

⁷⁶ OH GMC/GPhC 10th January 2019.

⁷⁷ The [summary of requirements for the NHS and clinicians](#) can be found on the [NICE interventional procedures guidance webpage](#).

⁷⁸ NICE written evidence to the Review.

procedures should factor in the particular responsibilities of clinicians and organisations to monitor risks during this period, including the training time taken to acquire the necessary competencies and skills.

Quality Assurance across the System

- 2.75 Assurance is a process by which the performance of organisations is assessed against set standards. The written and oral evidence we received paints a complex picture of the assurance of healthcare providers. NHS England sets the templates for standardised national contracts for commissioning, which Clinical Commissioning Groups (CCGs) adopt locally. NHS England also lead work on the GP contract and the Community Pharmacy Contractual Framework. The performance of these bodies is assured through specific frameworks such as the NHS Oversight Framework (previously the Improvement and Assessment Framework) for CCGs. Primary care is assured by the CCG and the CQC. The Quality and Outcome Framework also rewards GPs for the quality of care they provide. Pharmacies are assured through the Community Pharmacy Assurance Framework, and through inspections by the GPhC. The MHRA is responsible for determining whether a device or medicine remains available following instances where – although it has been used appropriately – there has been a negative outcome (e.g. an adverse reaction to a medication or a device is faulty). The patient safety team (which was in NHS Improvement⁷⁹) have a role in acute events when there is an inappropriate use of a device or medicine, or its use falls outside the remit of the regulator.⁸⁰
- 2.76 From this evidence it was not clear to us that any of these assurance mechanisms would have been able to detect the issues in the interventions under review. Keith Willett of NHS England accepted that there must be improvements on how the system recognises ‘*a rising tide of events*’ as in the case of mesh and valproate.⁸¹ We also spoke to the DHSC about the large number of organisations who have regulatory responsibility in the NHS, oversight and cross-connection between these organisations. They recognised the need for improved work across these organisations to monitor and co-ordinate action. Sir Chris Wormold, Permanent Secretary at the Department of Health and Social Care, told us: ‘*I do think creating things which are not the executive manager of the system but whose job it is to scan the whole horizon – in the way that we want the National Patient Safety Director to do – is very important.*’⁸² Although this role brings together work from other

⁷⁹ Note, on the 1st April 2019, during the data collection period of the report, NHS England and NHS Improvement have come together to act as a single organisation.

⁸⁰ NHS England.

⁸¹ OH NHSE 14th February 2019.

⁸² OH DHSC 2nd May 2019.

bodies, it does not have a remit for long-term adverse outcomes, such as those under review.⁸³

- 2.77 Assurance is an important part of ensuring a system is performing as expected. Assurance processes on their own may not recognise new problems, or guarantee patient safety. There are limitations, such as quality of data collection, lack of oversight, and powers of enforcement. Even when all the actors behave within their remit, the desired outcome might not be achieved. This brings us to our final point on assurance. **When the system has monitored guidance or standards, and identified an issue, there must be clarity on who is responsible for co-ordinating action, and there should be sufficient support and resource for implementation of remedial action.**

Theme 9: 'Collect once, use often' – Data capture and the electronic record

'Collect once, use often...'

Matt James, CEO of the Patient Healthcare Information Network (PHIN)

- 2.78 We commented in Chapter 1 that the healthcare system collects a huge amount of information. Yet it could not provide us with the answers we needed to assess the scale of the problems we were asked to look at. Either the information was not available because it had never been collected or because it was in a format that could not be linked to give us the answers we sought.
- 2.79 Electronic data capture matters if the healthcare system is to be able to map intelligently longitudinal patient care pathways, which track patients through a lifetime of health service interventions. This data can then be interrogated to discover what works, the true nature and rates of long term adverse outcomes, can help audit best practice, and can identify clinical outliers as a means of improving healthcare provision for all.
- 2.80 Professor Keen explained to us that NHS IT systems and the way they currently capture data does not make this interrogation easy. *'Key data about patients, procedures, medications, incidents and adverse outcomes are captured by different people and recorded in different places... different combinations of data are provided to and managed by different sets of clinicians and managers, thus no one*

⁸³ OH NHS Improvement 26th March 2019.

*group has effective oversight. And this fragmentation applies to regulators, each of which uses different subsets of data’.*⁸⁴

- 2.81 We also have the problem of whether all the right data is collected. A number of those who gave evidence spoke of the importance of collecting far more widely and routinely than at present, improvement in health outcomes as perceived by the patient – in particular Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs). Widespread use of both could help identify problems at an early stage through structured data collections, especially when used in combination with a register of devices, procedures or medications. Yet despite the contribution these measures can make, we were told that PROMs collections are mandated for just two procedures at a national level (primary hip and knee replacements). In practice, though, there are other outcome measure collections taking place in more-or-less nationally co-ordinated ways.⁸⁵ In our view **these patient-reported measures should be used far more widely and become common currency in the assessment of the benefits and risks of current and new interventions.**
- 2.82 There is a universal consensus that any change to the data healthcare providers are required to collect on behalf of regulatory bodies carries huge resource implications. We do not underestimate this - indeed we wholeheartedly support the ‘*collect once, use often*’ approach to data collection. **As a minimum every interaction the patient has with a health service provider should be captured once by one or other data subset, ideally in the electronic health record, with the NHS number acting as the consistent data field that enables those subsets to be linked.**
- 2.83 It took more than two decades before the teratogenic harmful effects of sodium valproate were fully recognised and understood. Neurodevelopmental delay, a recognised characteristic of Foetal Valproate Spectrum Disorder (FVSD) by its nature will not become apparent for some years after the birth of a child born to a mother on Valproate and may not be properly assessed until the child reaches primary school age.
- 2.84 The Expert Working Group (EWG) set up to advise on better ways to collect and monitor data on the safety of medicines in pregnancy – itself a recommendation of the EWG on hormone pregnancy tests (HPTs) – recognises the need to consider both physical and neurodevelopmental malformations in determining whether a medication is safe. **In our view the most effective, least burdensome way of**

⁸⁴ Professor Justin Keen, Ms Julia Lake, Dr Susan Partridge, Dr Rebecca Randell written evidence.

⁸⁵ The National Joint Registry, for example, supports routine collection of PROMs on hip, knee and shoulder replacements. For privately funded healthcare, PHIN is implementing a programme encompassing outcomes measures for 13 common procedures.

collating data on the latter would be to extend the reach of the identifying NHS number of every child by ensuring it is entered on their school attainment record. In this way, and with the means we now know exists to link electronic data records, we can and should go wider than the healthcare system to answer the question ‘Is this drug safe for use in pregnancy?’⁸⁶

Theme 10: ‘Collecting what matters’ – Databases and Registries

‘The one thing that would make the difference moving forward is if we had robust, rigorous, interrogable systems for recording the outcomes not only of devices... but actually of procedures that we do to people...’⁸⁷

Professor Kevin Harris, NICE

- 2.85 In 2003 NICE first recommended that observational data on the effectiveness and safety of TVT mesh for the treatment of SUI be collected over a period of 10 years or more, preferably nationally and coordinated in the form of a registry of audit data. This did not happen. We were told that one of the problems was assuring universal compliance.

Distinction between a Database and a Registry

‘...compulsion, I’m afraid, is the only way forward for registries and audits...’⁸⁸

Professor Derek Alderson, President, Royal College of Surgeons

- 2.86 Pivotal to our thinking on how to prevent harm in the future is the establishment of patient-identifiable registries for new devices and medicines that can be interrogated over time to assure long-term efficiency and to detect harm. We have investigated and listened carefully to the evidence from those who manage databases/registries currently in operation.⁸⁹ We have also taken expert advice on the implications of the General Data Protection Regulation [2018](GDPR) as currently understood.

⁸⁶ See also Law, D et al. ‘Safeguarding Children and improving their care in the UK’ The Lancet 25 July 2015: 386 [https://doi.org/10.1016/S0140-6736\(15\)00538-3](https://doi.org/10.1016/S0140-6736(15)00538-3)

⁸⁷ OH NICE 14th February 2019.

⁸⁸ OH Royal College of Surgeons 7th February 2019.

⁸⁹ National Joint Registry, UK Epilepsy and Joint Registry, Breast and Cosmetic Implant Registry (BCIR), the National Congenital Anomaly and Rare Disease Registration Service.

2.87 This leads us to conclude that legitimacy under GDPR requires a separation of:

- i. a ‘database’ that can be legally mandated in the public interest to hold a limited patient-related dataset. This should include the patient’s NHS number, their date of birth and gender, the unique device identifier (UDI), the name and GMC registration number of the operating surgeon, the health care provider and the date of the procedure;
- ii. a ‘registry’ that would act as a repository for more complex patient related information datasets enabling research and investigation into patient outcomes.

This would require patient consent.

2.88 We propose, and have tested out, the following definitions of both with a range of NHS and private healthcare stakeholders. None sought to contest these.

- A database:⁹⁰ a structured set of data held in a computer, especially one that is accessible in various ways.
- A Registry:⁹¹ an organised system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to a particular medical device(s) at a reasonably generalised scale (e.g. national, regional, health system) with a primary aim to improve the quality of patient care.

Databases

2.89 It is our view that every relevant surgical procedure for the treatment of SUI or POP – using mesh implants or not – should be entered on to a national database. The data fields we propose feature routinely in the treating surgeon’s operation note so should pose no new data collection burden. The scan4safety programme has shown that the technology exists to create a medical devices database that records the UDI for each device. To move towards one hundred percent compliance across the NHS and private sector requires the collection of this data to be mandated by the Secretary of State for Health and Social Care. As this mandate or direction overrides a patient’s right to opt out of their personal data being shared it is only reasonable that the data collected for the database is the least necessary to fulfil its legitimate purpose.

⁹⁰ Oxford dictionary.

⁹¹ **International Medical Device Regulators Forum:** Tools for Assessing the Usability of Registries in Support of Regulatory Decision Making, 27th March 2018.

- 2.90 We are hugely encouraged that our ideas have been persuasive. In November 2019 we met the Secretary of State for Health and Social Care and discussed the urgent need for the database to be established. He supported our proposal and issued a Ministerial Direction mandating the capture of this information by NHS Digital in a single database. We fully endorse this, as in our view NHS Digital is best suited to ensuring adherence to a common set of data standards, error minimisation and close on 100% coverage. The database will initially be designed for mesh procedures. Over time this would extend to all procedures involving devices and implants and, for comparative purposes, to relevant clinical activity for the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse that does not involve a surgical device or implant.
- 2.91 We understand that NHS Digital will start the mesh data collection later in 2020. Priority should be given to capturing the data fields from the newly launched mesh complication centres and those healthcare providers wishing to resume mesh implant surgery, should all the conditions for lifting the pause be met and the decision taken that it is safe to do so. **Databases and subsequent registries should embrace the private or independent health care sector as well as the NHS.**
- 2.92 We also wish to see the establishment of a database of all women of child-bearing age who are taking sodium valproate. We are deeply concerned that decades after the risk was first understood babies with disabilities continue to be born to mothers who have taken valproate during pregnancy without being aware of the risks. A database is one measure urgently needed to enable women to be contacted and then properly informed and, where necessary, reminded of the risk (see Chapter 4, paragraphs 4.96 – 4.97).

Registries

'I've been on the edge of the registry debate for most of my professional life. I think we have got to find the right balance between collecting enough that we can be reasonably go back to patients if we have a concern. One of the first emergencies I had to deal with was the PIP breast implants. We didn't know who had had what...'⁹²

Dame Sally Davies, former Chief Medical Officer, DHSC

- 2.93 Registries are important. They give unparalleled opportunities for research and audit, enabling policy makers, regulators, health care providers and clinicians to monitor long term outcomes and report on whether health care is safe and effective.

⁹² OH DHSC 2nd May 2019.

- 2.94 Until now registries have been limited and niche, focussing on defined diseases, conditions or particular devices. All too often their creation has been driven by catastrophes. In the UK the metal on metal hip disaster prompted the development of the National Joint Registry (NJR), now considered a leader in its field; the PIP breast implant scandal led to the development of the Breast and Cosmetic Implant Registry run by NHS Digital. This should not have been the case nor should it be in the future.
- 2.95 Those we have spoken to recognise the benefits that a mature registry can deliver. Yet we have observed a system-wide inertia that until recently has stifled their proactive development for both pelvic mesh and anti-epileptic medications and for devices and medications more broadly.
- 2.96 The registry, as we have defined it, is a repository of more complex information necessary for evaluating long term outcomes and patient safety. It requires patient consent under GDPR. If that consent is explicitly given and the activities of the Registry are transparent and adequately explained to the patient in advance (of each surgical procedure) it would allow Registry administrators when required, to contact the patients. The information collected by Registries is not just clinically coded but will also often include patient sensitive information including PROMs and PREMs. They therefore have to be individually designed by patients and clinicians working together.
- 2.97 There is no specific PROM for mesh complications. The need for one was raised in November 2018.⁹³ To provide useful information PROMS should be validated to ensure they collect the correct information. We realise that validation takes time. In the absence of a mesh-specific PROM it has been suggested that other validated PROMS for other indications, such as SUI and pelvic pain be used. This is a pragmatic solution, but we are disappointed by the lack of urgency. We would encourage, under the aegis of specialist societies such as British Association of Urological Surgeons (BAUS), British Society of UroGynaecology (BSUG) and the Pelvic Floor Society (PFS) that the design and development of a mesh specific PROM is urgently undertaken, and this could be hosted by HQIP.
- 2.98 In addition to databases leading to the development of registries for pelvic mesh and new medical devices, (**Chapter 1, Recommendation 7**) we also wish to see a similar approach to valproate and other anti-epileptic medications. Valproate was known to be teratogenic at the point it was first licensed in 1972. The first and only UK registry to capture data on the effects of valproate among other anti-epileptic

⁹³ This was raised at the Health Quality Improvement Partnership (HQIP) meeting on the feasibility of an interim database.

drugs (AEDs) on pregnancy came into existence in the mid 90s.⁹⁴ It has achieved much to close our knowledge gap but it has its limitations. It is entirely voluntary; at its peak it captured 30% of pregnancies for women with epilepsy and it follows those pregnancies for only three months post birth. At best it is concerned with early presentation of physical malformations. We were told *'It's run on a shoe stringone part time nurse really runs the whole thing.'*⁹⁵ This is simply not acceptable.

- 2.99 We want to see a registry for all women on anti-epileptic drugs who become pregnant, to include mandatory reporting and data relating to them and their child(ren) collated over lifetimes. This should not be limited to sodium valproate, but should also include all AEDs. We have heard from patients and experts who are concerned that the long-term outcomes of the newer generation of AEDs are not yet known (see Chapter 4, paragraphs 4.91 – 4.92).
- 2.100 In the case of medicines this is easier to establish, as a database for all NHS prescriptions are included in a national database for payment purposes and we have discussed with NHS England the use of this database in order to contact directly women of child bearing age who are currently taking valproate.

Registry funding

- 2.101 Early consideration should be given to how the detailed and more complex registries as opposed to the databases, are to be funded. Comparators both here and abroad are mixed. Some are publicly funded, others like the NJR are self-financing through an industry funded levy. We do not in principle favour one over another. However, feedback from a mature well run registry benefits patients above all as well as industry and the healthcare system. Thus an NHS contribution is appropriate. In addition an industry-funded model must go hand in hand with governance arrangements that emphasise a complete separation of funding and operational decision making.
- 2.102 The priority is to get these registries up and running. The DHSC may wish to do this through a next steps agency like HQIP⁹⁶. Mesh-affected patients and those on sodium valproate have waited too long for answers. They want to know that data is being captured now that will help answer the question *'is this device or is this medication safe?'* Progress on the development of these databases and associated registries is long overdue and the system must take responsibility for that. Funding issues cannot be the cause of further delay.

⁹⁴ The UK Epilepsy and Pregnancy Register <http://www.epilepsyandpregnancy.co.uk/>

⁹⁵ OH UK Epilepsy and Pregnancy Register 14th March 2019.

⁹⁶ HQIP report 'Proposal for a Medical Devices Registry', February 2020 <https://www.hqip.org.uk/resource/proposal-for-a-medical-devices-registry>

Theme 11: ‘Time to change focus’ – Regulation of medicines and devices and potential reforms

2.103 The current regulatory system has been a recurring area of concern for patient groups across all three of our interventions. We recognise that the current pharmaceutical and devices regulatory systems have gaps and inefficiencies in:

- being fully transparent in all their operations;
- systematically evaluating outcomes;
- delivering real-time risk assessment based on all relevant sources of evidence including patient experience;
- including risk management tools validated by behavioural science;
- incorporating current best practice in risk communication.

2.104 These deficits need to be addressed in the most appropriate evidence-based way. The regulatory system should become a learning system with continual monitoring and updating of its practices. Research into the effectiveness and impact of the way in which the MHRA carry out their regulatory duties is essential, not least to restore trust in the system.

2.105 The regulation of medicines and medical devices in the UK has been governed by EU laws since it joined in 1973. As part of the transitional arrangements to leave the EU the UK will adhere to the EU regulations governing medicines and medical devices until the end of 2020. After that a new legal framework will be required for the operation of the MHRA. We recognised that once the UK had left the EU there was a unique opportunity to shape the UK regulatory agenda using what we had heard and learnt throughout this review. We outline high-level changes to regulation to strengthen patient safety:

- a. Establishing clear legal frameworks around safety-based decision-making which include the systematic involvement of patients and the public;
- b. Improving medical device regulation;
- c. Overhauling adverse event reporting to create a transparent, user-friendly system that recognises the contribution of those who make reports and engages with them throughout the analysis and decision-making process. There must be delineated obligations placed on manufacturers, healthcare professionals and the MHRA;

- d. Identifying risk profiles and teratogenicity for medicines used in pregnancy;
 - e. Developing a protocol for a prompt system-wide co-ordinated response to safety decisions related to a medicine or medical device.
- 2.106 Patients must be central to the workings of the MHRA. To involve them in a meaningful way will require changes in the design and operation of regulation— in strategy, systems design, and operation, and in listening and responding to safety signals. Adequate resource and expertise must be allocated to involving patients.

Including patients and the public in decision-making

- 2.107 The patient contribution must be taken seriously as an integral part of the process of regulatory decisions on significant safety and benefit risk issues. It is the patient who takes the medication or has the device and it is the patient who has the benefit and who lives with the consequences of any adverse events. This principle applies to all healthcare regulators and professionals. **However, as we go forward the MHRA are in a unique position of requiring a new legal framework and we strongly recommend that provisions are made for systematically engaging patients and the public. There should be a requirement on the MHRA to demonstrate how patient views have been taken into account and influenced the regulatory decision.** This mirrors existing EU provisions for medicines safety issues.
- 2.108 Our Review has highlighted the need for a strengthened legal framework for safety based regulatory decision-making. In our view when a medical device or medicine safety issue is raised the MHRA should be subject to binding timescales for decisions on risk management. Such timescales should be set according to the degree of public health urgency, as they are by the current EU framework. The MHRA should be obliged to publish performance data on these timescales and inform the Patient Safety Commissioner of non-compliance.
- 2.109 We believe there should be greater transparency of all regulatory safety decisions. Regulatory decisions should be published together with the fullest possible supporting evidence, evaluation (including all areas of uncertainty) and justification for actions.
- 2.110 When relevant to public safety the MHRA should have the legal authority to apply their decision about a given product to other products in the same class. Decisions about entire classes of product should be binding on all the manufacturers.
- 2.111 Where new safety information comes to light, information for patients should be provided or updated without delay, and the benefits and risks described in a way which will be understood by patients. Statements such as ‘benefit risk favourable’ should be replaced with more understandable information on BRAN – benefits,

risks, alternatives or deciding to do nothing. Care should be taken to ensure that the content is unambiguous and the presentation is accessible.

- 2.112 Annex G Pelvic Mesh Supporting Information details MHRA decisions on mesh and those of other major international medical device regulators. Devices and medicines are global industries, and it seems counterintuitive that one country can consider a product safe for use when another does not. We recognise that the situation in the UK is unusual, in particular the interplay between MHRA and NICE. In our opinion **it would greatly aid public understanding if the MHRA gave detailed reasons for its decisions if they differ from decisions made by another major international regulator.**

Improving Medical Device Regulation

- 2.113 Implementation of the EU Medical Devices Regulation (MDR) has been delayed,⁹⁷ as such the UK will not implement it during the transition period. We have assumed the UK will adopt the MDR's more stringent standards, and we outline areas where the UK could make further improvements.
- 2.114 At present the MHRA only maintain a list of devices at the lowest risk (Class I). They do not maintain a list of medium to higher risk devices (IIa, IIb and III). This is a function of current EU device regulatory structure. The MHRA may only find out a device is being used in the UK if there is a problem with that device. **A register of devices similar to the Australian Register⁹⁸ should be created and maintained by the MHRA (Chapter 1, Recommendation 6).** This will make it possible to know which devices are (or were) on the UK market at any given time. Entry on the register should be a condition for selling in the UK, with the MHRA able to de-register devices and remove them from sale if necessary. We propose that manufacturers would need to apply to the MHRA, including detailing any authorisation (or refusal to authorise) that they hold for that device in other jurisdictions and their vigilance plans. If the MHRA deem the application acceptable the device can be entered on to the UK devices register. Under these proposals the **MHRA's role would be more akin to a licencing authority than it has to date, with a greater emphasis on vigilance (Chapter 1, Recommendation 6)** and follow up. **The DHSC should consider if an equivalent of the Commission on Human Medicines is needed for devices.**

⁹⁷ https://ec.europa.eu/info/sites/info/files/proposal_for_a_regulation_of_the_european_parliament_and_of_the_council_amending_regulation_eu_2017_745_on_medical_devices_as_regards_the_dates_of_application_of_certain_of_its_provisions.pdf

⁹⁸ <https://www.tga.gov.au/searching-australian-register-therapeutic-goods-artg#about>

- 2.115 As a country with a comprehensive national health service we have an opportunity to track devices using post-marketing vigilance. A database of implanted devices and linked specialist registries will allow long-term follow up of patients and provide information on both device safety and patient reported outcomes, including those that become apparent after several years (**Chapter 1, Recommendation 7**). The information gained has advantages for patients, the healthcare system, the MHRA and manufacturers. A difficulty with adverse device reports about implantable devices is that the person making the report may not know which device was implanted. The onus is on the patient to retain any information supplied at the time of surgery and to report it correctly. In future, with appropriate permissions, **an adverse device report could be linked to the patient-identifiable database of implanted devices**. This would accurately identify the device, without increasing the demands on the person reporting.
- 2.116 Unique Device Identifiers (UDI)⁹⁹ are alphanumeric identification codes for medical devices. There is a UDI catalogue in the US (GUDID),¹⁰⁰ which is an accessible source of information on device characteristics, storage, handling and, importantly, premarket submissions including safety data. The EU devices database, (EUDAMED) is not currently operational and will not be so for some time. **A public-facing UDI database for UK devices based on GUDID should be scoped**. Interoperability with international regulator systems should be maximised to reduce data entry burdens.

Adverse Incident Reporting

- 2.117 The UK is no longer part of the pan-European pharmacovigilance monitoring, but remains actively involved. UK reports are submitted to the World Health Organisation (WHO) and the UK has access to all the reports submitted to WHO. All EU pharmacovigilance reports are also submitted to the WHO, so the UK is still able to access, analyse and assess reports from across the EU.
- 2.118 Underreporting of drug adverse reactions is an endemic world-wide problem. Spontaneous reporting is imperfect, but it is important and should be supported and encouraged. We have heard how the Yellow Card system has evolved and been improved, including the addition of an app.¹⁰¹ We have also heard from women who have been unable to update their Yellow Card reports at a later date when symptoms change. We understand that the MHRA are working to correct these issues.¹⁰² However, despite its long history, the Yellow Card system is not well

⁹⁹ UDI are made up of a device identifier (DI) specific to that device version/model and a product identifier (PI). DIs are a constant way to identify that device, PIs specify product details such as expiry date, lot number, etc.

¹⁰⁰ Global Unique Device Identification Database <https://accessgudid.nlm.nih.gov/about-gudid>

¹⁰¹ <https://yellowcard.mhra.gov.uk/>

¹⁰² OH MHRA 10th January 2019.

recognised or routinely used. Even among healthcare professionals, awareness must be improved, and effective ways to increase understanding and encourage reporting should be implemented.

- 2.119 Collectively patients now make more Yellow Card reports than any other group.¹⁰³ Any actions to facilitate this should be encouraged. For example, a QR code or other identifier on the patient information leaflet (PIL) which could interact with the Yellow Card app to autofill some of the information would make the reporting easier and guarantee higher quality inputs.
- 2.120 There should continue to be legally mandated reporting of adverse incidents relating to medical devices and medicines by all healthcare organisations to the regulator within a timeframe commensurate with the potential harm. The MHRA should evaluate each organisation's reporting and any concerns could be raised with the Patient Safety Commissioner.
- 2.121 In their oral evidence the MHRA said that they had pressed for publicly available adverse device reports, but that other EU states had been unwilling to add this into the MDR.¹⁰⁴ **We recommend a publicly searchable database including all adverse events for both medicines and devices.**¹⁰⁵

Risk profiles for medicines used in pregnancy and identifying teratogens

- 2.122 The risk of teratogenicity has meant women are largely excluded from clinical trials; as a result only a handful of medicines are licensed for use in pregnancy and the safety profiles of newer medicines in pregnancy are initially unknown. Indeed, the whole pharmaceutical and devices regulatory systems have been criticised as being sub-optimal for women. There are moves to change this nationally and internationally.¹⁰⁶
- 2.123 Certain medicines with known risks have risk mitigation strategies in place, such as the valproate PPP, which arose from a European Medicines Agency (EMA) review and is an EU wide requirement. The MHRA have been very clear that the UK will continue with the valproate PPP after we have left the EU. **It is important that the**

¹⁰³ MHRA written evidence to the Review.

¹⁰⁴ OH MHRA 27th February 2019 Session 1.

¹⁰⁵ The US FDA have a publicly searchable database, MAUDE – **M**anufacturers, and **u**ser facility **d**evice **e**xperience <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>

¹⁰⁶ For example, see John Naish 'The everyday medicines that make women ill because they have only been tested on MEN' Daily Mail 5 November 2012; Amy Westerveldt 'The medical research gender gap: how excluding women from clinical trials is hurting our health' The Guardian 30 April 2015; Simon Crompton 'Why the drugs don't work for women and what to do about it' The Times 2 July 2019.

MHRA continues to be aware of any risk mitigation strategies put in place in other countries, including the EU and wider afield, and gives them due consideration.

- 2.124 It is clear to us that there needs to be better tracking of adverse events, particularly teratogens. We welcome the Expert Working Group on use of Medicines in Pregnancy. We have heard from the National Congenital Anomaly and Rare Diseases Registration Service (NCARDRS) who have told us that the tracking of physical anomalies has improved considerably over the years.¹⁰⁷ NCARDRS now have a nationwide scheme for registration of physical congenital anomalies as well as for rare diseases.¹⁰⁸
- 2.125 The identification of neurodevelopmental issues has been largely driven by dedicated researchers and clinicians carrying out individual assessments of affected individuals. Such assessments are costly and time consuming, but they are essential and should be properly resourced.¹⁰⁹ In addition system-wide data analysis should be used to detect signals. For example, once the NHS number is within educational records any medicine suspected of impacting on cognitive development could be assessed by analysing the educational records of exposed children (see paragraph 2.84). Where particular medications are suspected of being detrimental to neurodevelopment we would expect manufacturers to fund horizon scanning initiatives and, if required, more detailed studies on an arms-length basis. This approach will enable faster acquisition of medication risk profiles, helping to inform clinicians and women.

A prompt system-wide coordinated response to safety issues

- 2.126 As discussed in paragraph 2.76, prompt co-ordinated response by the healthcare system to safety issues over medicines or medical devices is needed. **This calls for the setting up of a system-wide healthcare intelligence unit to facilitate early signal detection which would draw on various sources of information** including for example databases and registries, pharmacovigilance and issues raised by the Patient Safety Commissioner (see **Chapter 1, Recommendations, 2, 6 and 7**). Building on that, a protocol should be established which details the roles, responsibilities and powers of the healthcare organisations required to effect a co-ordinated response when a safety decision based on new evidence of harm is taken

¹⁰⁷ OH NCARDRS 5th March 2019.

¹⁰⁸ Similar schemes operate in other devolved nations; the congenital anomaly register and information service (CARIS) in Wales and the congenital anomalies and rare diseases registration and information service for Scotland (CARDRISS).

¹⁰⁹ We note that in their oral evidence Sanofi told us that they funded these type of studies and we fully recognise the benefit that arms-length industry funding can bring in these situations, OH Sanofi 18th January 2019.

by the Licensing Authority (Health Ministers) or relevant others. This response should include:

- a. the ability to contact and call in individual patients if necessary;
- b. co-ordinated update and re-issue of clinical guidelines by NICE;
- c. duty on the CQC to follow-up the relevant healthcare organisations which are using the specific medical device or medicine;
- d. duty on the professional regulators (GMC, GPhC) to review evidence of compliance in individual revalidation appraisal.

Theme 12: Patient safety – doing it better

‘[This] ... is the story of a healthcare system which proved itself dysfunctional at almost every level when it came to keeping patients safe...’¹¹⁰

Paterson Inquiry

- 2.127 In this chapter on overarching themes, we have considered issues that speak directly to the concerns that affect individual patients and to the deficits that are system wide. In this final section we bring the two together. As we have seen and heard, all too often patient reports of harm are either not listened to or are dismissed as subjective, unscientific and anecdotal. But they are also sporadic, made to different bodies at different times, usually uncoordinated and may provide inconsistent evidence. Identifying and responding to adverse trends from a dispersed set of reports, even if those reports are taken seriously, can be difficult. This is especially so if those bodies receiving the reports have limited requirements to communicate with each other let alone to work co-operatively to address the problem.
- 2.128 In our oral evidence sessions we asked the regulators and the arms-length bodies – both professional and systems regulators including the MHRA, NICE, CQC and NHS England and Improvement - and DHSC – if they could explain how what we had found in our Review had happened. They could not assist us. Each worked within the remit required of them. The linkages between them and the oversight of the system as a whole had not worked. Those we spoke to recognised the need for, and the complexities of achieving, a properly co-ordinated response but this

¹¹⁰ Report of the Independent Inquiry into the Issues raised by Paterson (February 2020) available at <https://www.gov.uk/government/publications/paterson-inquiry-report>

had not been deliverable from within a fragmented healthcare system, despite numerous initiatives.

- 2.129 We have seen that regulation has not worked well enough; nor does the complex and disparate complaint system provide the answer. We need to try a different approach and one that does not involve yet another re-organisation of the health service. For, as Dr Aidan Fowler, the National Director of Patient Safety, commented *'...organisational change is a major distraction and each time it occurs there is a loss of pace.'*¹¹¹ We wholeheartedly agree.
- 2.130 We support many of the system's new initiatives. We support the new and extended remit of what was the National Patient Safety Agency, now lodged within NHS England and NHS Improvement (NHSE&I) under the leadership of Dr Fowler. But as Dr Fowler told us, his organisation has no remit for minimising the risk of long-term chronic adverse outcomes arising from the implanting of mesh or from taking sodium valproate.¹¹² We recognise the purpose of the existing organisations, such as the MHRA and NICE and we do not want to suggest that these should be replaced though we recommend changes that would make them more effective and accessible. We also believe the involvement of the professions, both in the regulation of their professional bodies alongside patients and in the systems regulators such as the CQC is important. We support the work of the Health Care Quality Improvement Partnership (HQIP) and recent initiatives by NHSE&I towards the development of new comprehensive databases and registries to record and analyse outcomes.
- 2.131 But the experience of the last two decades and what we have heard suggests this will not be enough. The healthcare system, and DHSC in its oversight role, has failed to demonstrate it can both recognise system-wide shortcomings and remedy them. Far more is needed to sharpen the linkages between the system's constituent parts to deliver system wide responses to patient safety concerns that are adequate, robust and timely.
- 2.132 We argue that to do this we need a new voice, that of a newly created Patient Safety Commissioner, an independent and proactive public leader with a statutory responsibility to champion the value of listening to patients and promoting users' perspectives in seeking improvements to patient safety. This role would sit outside the current patient safety system, accountable to Parliament through the Health and Social Care Select Committee, not to government and not to the devolved NHS management system. We are calling for a public spokesperson with the necessary

¹¹¹ OH NHS Improvement 26th March 2019.

¹¹² *ibid.*

authority and standing to talk about and report on, to influence and cajole where necessary without fear or favour on matters related to patient safety (**Chapter 1, Recommendation 2**).

- 2.133 Through her/his work, the Commissioner would identify steps that need to be taken to improve patient safety around the use of medicines and medical devices and encourage other organisations to act. S/he would provide a means of holding the current system to account on behalf of patients for delivering necessary improvements in patient safety. S/he would do what we as a Review have already started to do – listening to patients and engaging with those whose job it is to act in order to press for changes that will minimise risk of harm. It is our fervent hope that the Patient Safety Commissioner will pick up where we finish.
- 2.134 The role will bring a unique and focused perspective to efforts to improve patient safety that complements the work of current organisations and agencies, while also addressing our concerns about the timeliness and coordination of action on adverse consequences that patients have repeatedly raised. It offers the opportunity to build directly from patients’ experience and secure systemic improvement.
- 2.135 The primary statutory function of the Patient Safety Commissioner would centre on the aims of:
- promoting and improving patient safety, and
 - promoting the views and interests of patients and other members of the public in relation to the safety of medicines and medical devices.
- i. The Commissioner’s role would be designed to operate flexibly and prioritise her/his work so that s/he does not duplicate activity being undertaken elsewhere in the system, while also advising and recommending actions where they are needed.
 - ii. The Commissioner would set her/his own priorities and determine the appropriate response. This would be based around a core set of statutory Principles of Better Patient Safety which describe patient safety outcomes that matter to patients and other members of the public.¹¹³ The Commissioner would be required to develop these, involving patients and other members of the public from the outset.

¹¹³ This proposal mirrors approaches of other independent oversight bodies. For example, the Professional Standards Authority, has a general function to promote the interests of patients and is subject to a requirement to (among other things) demonstrate this general function through its statutory function of ‘the formulation of principles relating to good professional self-regulation’. For the Children’s Commissioner, the UN Convention on the Rights of the Child (UNCRC) provides a core set of values that performs a similar (but not identical) role. The Legal Services Board is bound by eight statutory regulatory objectives.

- iii. The Commissioner would be open to receiving direct reports from patients and other members of the public. Arrangements could be made to relay those direct reports to other organisations as appropriate. The Commissioner would retain an interest in how reports are handled, including in patterns in reporting and their outcomes.
- iv. The Commissioner would be able to obtain relevant information relating to patient safety concerns from other organisations. This would include, for example, reports relating to the safety of medicines and medical devices from the National Guardian (Freedom to Speak Up) and reports from whistle-blowers.
- v. The Commissioner would be required to operate under a statutory duty to involve and inform patients and other members of the public. It would be for the Commissioner to account for how this duty is met using a range of different approaches.
- vi. The Commissioner would have a general statutory power *‘to do anything which appears to it to be necessary or expedient for the purpose of, or in connection with, the performance of its functions.’*¹¹⁴ Giving the Commissioner the power to bring matters to the attention of both Houses of Parliament and the Secretary of State for Health and Social Care would provide a proportionate and focused means of highlighting where improvements are needed.¹¹⁵
- vii. Finally, it would be for the Commissioner to determine, once in post, what if any additional powers might be needed to fulfil her/his role. This could include a statutory duty to co-operate on all the constituent bodies of the health care system that have a remit for patient safety.

2.136 For a fuller description of these functions and activities and the governance arrangements needed to support the role see Appendix 2.¹¹⁶

¹¹⁴ Extract from Section 26(1) NHS Reform and Health Professions Act 2002 relating to powers for Professional Standards Authority for Health and Social Care.

¹¹⁵ The Children’s Commissioner can bring matters to the attention of both Houses of Parliament, as well as advising bodies on how they can act compatibly with the UNCRC. If a Children’s Commissioner’s inquiry report makes a recommendation to a body ‘undertaking a function of a public nature’ it can require an action plan in writing from that body through section 3(7) of the Children Act 2004.

¹¹⁶ We would like to acknowledge the work of Harry Cayton and Kate Webb in assisting us in our development of the Patient Safety Commissioner role and supporting governance arrangements.

Recommendations and Actions for Improvement	
Theme 3: Informed consent	
Information should be conveyed to patients in a way that is clear and meaningful. The opportunity to speak to, or hear from, others who have undergone the same intervention should be considered.	2.21
A single patient-decision aid (or core set of information) should be produced for each surgical procedure or medical intervention, co-designed by patients and clinicians. NICE should take the lead on facilitating this.	2.22
Patient-clinician consultations about consent must be proportionate to the circumstance and appropriately documented. Both the patient's and clinician's concerns and comments should be recorded. Where appropriate and with the agreement of both parties, conversations around consent should be audio or video recorded to allow the patient to take it away and reflect upon it. In future a copy of this discussion should be stored on the patient's electronic record.	2.24
Theme 4: Redress	
There is a need for additional training for those carrying out assessments for the Department of Work and Pensions (DWP) based on the insight condition reports. This should help those carrying out the assessments to make equitable decisions.	2.28
See Chapter 1, Recommendations 5	2.31
See Chapter 1, Recommendations 4	2.33
See Chapter 1, Recommendations 3	2.37
Theme 5: Complaints	
Patients across the NHS and private sector must have a clear, well- publicised route to raise their concerns about aspects of their experiences in the healthcare system. It will be for the implementation task force (see Chapter 1, Recommendation 9) to address this problem.	2.42
The time bar on GMC investigations should not be a barrier to establishing a pattern of poor practice by any one clinician.	2.43
The bodies that have received complaints about the interventions under review should reassess what they have been told and satisfy themselves that they have taken necessary steps to identify any patterns and trends. They should inform the relevant organisations and Patient Safety Commissioner of outcomes of concern.	2.44
Organisations who take complaints from the public should designate a non-executive member of the board to oversee the complaint-handling processes and outcomes, and ensure that appropriate action is taken.	2.45

Recommendations and Actions for Improvement	
Theme 7: Conflicts of interest	
Clinicians: See Chapter 1, recommendation 8	2.56, 2.58
Organisations: Organisations should ensure clear governance arrangements to cover the potential conflicts of interests of any individual who participates in either regulatory activities or inquiries, including the composition of expert panels. Whilst it is to be expected that those people asked to participate should declare any potential conflicts of interest, the organisation itself has a responsibility to make its own enquiries.	2.64
Manufacturers: See Chapter 1, Recommendation 8	2.65
Research: All journals should provide assurances to their readers that their Code of Practice relating to Conflict of Interest is compliant with the policy set out by the World Association of Medical Editors.	2.67
Theme 8: Guidelines: implementation and assurance	
Annual appraisal of doctors should include providing evidence of awareness of relevant guidance in the doctor's area of practice. Colleagues should report failure to follow guidance which is detrimental to patient safety. This should apply in the private or independent sector as well as in the NHS.	2.69
The GMC should be alert and act if any doctor's practice causes concern in respect of failure to follow guidance.	2.70
Hospitals should encourage clinical audit and should have robust systems for monitoring quality at Board level. The CQC should also assure itself that hospitals, both in the NHS and in the private sector, have robust quality assurance programmes including following appropriate guidance.	2.71
Those responsible for introducing new procedures should factor in the particular responsibilities of clinicians and organisations to monitor risks during this period, including the training time taken to acquire the necessary competencies and skills.	2.74
When the system has monitored guidance or standards, and identified an issue, there must be clarity on who is responsible for co-ordinating action, and sufficient support and resource for implementation of remedial action.	2.77
Theme 9: Collecting and using data	
Patient-reported measures such as PROMs and PREMS should become common currency in the assessment of the benefits and risks of current and new interventions.	2.81

Recommendations and Actions for Improvement	
Every interaction the patient has with a health service provider should be captured once only, and by one or other data subset, ideally in the electronic health record. The NHS number should be included to enable those subsets to be linked.	2.82
Every child's NHS number should be entered on their school attainment record on year of entry.	2.84
Theme 10: Databases and Registries	
Databases and subsequent registries should include the private or independent health care sector as well as the NHS.	2.91
See Chapter 1, Recommendation 7	2.98
Theme 11: Regulation	
When making regulatory decisions on benefit and risk of medicines and medical devices, the MHRA should demonstrate how patient views have been taken into account.	2.107
To aid public understanding the MHRA should give detailed reasons for its decisions if they differ from decisions made by another major international regulator.	2.112
See Chapter 1, Recommendation 6	2.114
The DHSC should consider if an equivalent of the Commission on Human Medicines is needed for devices.	2.114
See Chapter 1, Recommendation 7	2.115
Where the patient gives permission an adverse device report should be linked to the patient-identifiable database of implanted devices.	2.115
A public-facing UDI database for UK devices based on GUDID should be scoped.	2.116
We recommend a publicly searchable database of adverse events for both medicines and devices.	2.121
In future we recommend careful consideration should be given to implementing risk mitigation strategies of international regulators on potential teratogens.	2.123
We recommend the creation of a system-wide healthcare intelligence unit to facilitate early signal detection which would draw on various sources of information.	2.126
Theme 12: Patient Safety	
See Chapter 1, Recommendation 2	2.132

3 Hormone Pregnancy Tests

'I can honestly say that my heart is broken at the outcome of those two tablets given to me by my doctor.'

Patient testimony from a mother who used an HPT

Introduction

- 3.1 From the 1950s to the 1970s Hormone Pregnancy Tests (HPTs) were used in the UK.¹¹⁷ By 1978 all HPTs had been withdrawn in the UK. Various medicines containing the same hormones remain available on prescription. The market leading HPTs were Primodos made by Schering¹¹⁸ and Amenerone Forte made by Roussel.¹¹⁹ Together Roussel and Schering held over 90% of the UK HPT market (see graph 3.1).
- 3.2 Since the late 1950s concerns have been raised that HPTs may be teratogens, drugs that can cause abnormalities in a developing baby. Various malformations have been linked to HPT use. This has remained a contentious issue since it was first raised.

HPTs

Primodos was the most commonly used HPT, but various brands and formulations were available. HPTs contained sex hormones, usually both an oestrogen (often ethinylloestradiol or EE) and a progestogen, though some were just a progestogen. If a woman was not pregnant she would have a period-type bleed a few days after taking the HPT; if she did not bleed she was pregnant.

Adverse effects that followed HPT use

We have been told of the following adverse impacts which affected individuals and families have attributed to HPT use:

¹¹⁷ Details on HPT active ingredients and dates of marketing is available in Annex E HPT Supporting Information.

¹¹⁸ Schering was taken over by Bayer.

¹¹⁹ Roussel were taken over by Sanofi.

Deaths – these included miscarriage, stillbirth, baby deaths; **Neural tube defects**, including spina bifida, hydrocephalus, microcephaly, anencephaly, paralysis; **Limb defects** – these were reported to affect arms and/or legs, including shortened limbs, missing limbs or parts of limbs, talipes and various missing and/or deformed digits; **Sensory deficits**, including deafness, blindness and mutism; **Sensory-motor disorders**, ranging from balance issues to profound disability; **Congenital heart defects** of various types including Tetralogy of Fallot, heart murmurs, septal defects, leaking valves, and transposition of the great vessels were reported; **Intellectual disability** – learning, speech difficulties, including being non-verbal in some cases, expressive aphasia, developmental delay, autism, and in some cases severe impairment; **Genito-urinary defects**, including hypospadias, undescended testes, aberrant penis development, cervical abnormalities (including later cervical cancer), bladder exstrophy, kidney issues and incontinence; **Dysmorphic facial features**, including cleft palate and lip, missing cranial nerves and facial palsy; **Digestive system and bowel issues**, missing spleen, missing gall bladder, obstructed oesophagus; missing oesophagus; trachea-oesophageal fistula, imperforate anus, chronic constipation, faecal incontinence, some individuals require to be tube-fed others require surgery; **Skeletal problems**, including additional ribs, hip dysplasia, under-developed stature, chest deformities; **Spinal issues**, for example scoliosis, additional vertebrae, shortened spine; **Seizures**.

In some cases individuals had one congenital anomaly, other individuals had multiple anomalies.

We were also told of **genetic conditions** such as Angelman Syndrome.

- 3.3 The Association for Children Damaged by Hormone Pregnancy Tests (ACDHPT) was set up in 1978 with four key aims: raising awareness of HPTs, providing support to families, obtaining a public inquiry and determining the culpability of the manufacturers, and to highlight what they saw as the failures of the regulators.¹²⁰
- 3.4 The energy and commitment of the ACDHPT campaigners over the years is impressive. We have been touched by the willingness of ACDHPT members to share their deeply personal and sometimes harrowing experiences. They have eloquently told us how their disabilities have shaped their lives physically and psychologically.
- 3.5 It is not our role to determine a causal association between HPT use and physical malformations. We have heard from members of the Expert Working Group on Hormone Pregnancy Tests (EWG), who concluded that the existing evidence does

¹²⁰ See 'Objectives of the Association for Children Damaged by Hormone Pregnancy Tests' in the EWG annex 'Documents submitted through the public call for information' available at <https://mhra.gov.filecamp.com/s/GZdoZEG9hoT4o6nZ/fo>

not support a causal association,¹²¹ but a possible association could not be ruled out. In contrast Professor Heneghan told us that his meta-analysis of the existing evidence showed a causal link.¹²² Neither the ad hoc EWG¹²³ nor the European Medicines Agency (EMA) review¹²⁴ supported the findings of Professor Heneghan's meta-analysis.

- 3.6 Our Review has a different, and in our view long overdue, purpose: to review the UK's decision-making around HPTs by the healthcare system, including the regulators and manufacturers. This will be considered in the context of the time as regulation has moved on in the 40 years since HPTs were withdrawn. It is important to note that for legal reasons asserted by Bayer, it has not been possible for the Review to provide the detail of certain documents in the report. This has meant that the Review has been limited in the extent in which it could set out the text or contents of these documents in its report, although it has read them and relied on them in coming to its findings. Additionally, Bayer has asked the Review not to publish or to provide links to the documents in question. See Appendix 4 – 'How we Worked', paragraph 65.
- 3.7 HPTs are not just a historic issue. We do not doubt the continuing psychological suffering caused by their use – indeed we have witnessed it on the faces and in the words of the families we have met; the sorrow and anger arising from a conviction that lives had been needlessly, and often irreparably, damaged, both physically and mentally; the impact of carrying a relentless sense of burning injustice for decades without resolution; parents of the affected children, deeply anxious about what will happen to their adult child when they are no longer there for them; mothers burdened by guilt at having taken the tablets. The extent of the suffering, endured over decades, must not be underestimated.

¹²¹ Report of the Commission on Human Medicines Expert Working Group on Hormone Pregnancy Tests 15 November 2017 available at <https://www.gov.uk/government/publications/report-of-the-commission-on-human-medicines-expert-working-group-on-hormone-pregnancy-tests>

¹²² Heneghan C et al. 'Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis' [version 2; peer review: 3 approved]. F1000Research 2019, 7:1725 <https://doi.org/10.12688/f1000research.16758.2>

¹²³ Report of the Commission on Human Medicines ad hoc Expert Group on Systematic Review and Meta-analysis of Oral Hormone Pregnancy Tests by Heneghan et al available at <https://www.gov.uk/government/publications/chm-ad-hoc-expert-group-evaluation-of-systematic-review-and-meta-analysis-of-studies-on-oral-hormone-pregnancy-tests-by-heneghan-et-al>

¹²⁴ Assessment report for Article 5(3) procedure: Norethisterone and ethinylestradiol (EMA/H/A-5(3)/1477) available at https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-norethisterone-ethinylestradiol-emea/h/53/1477_en.pdf

Hormone Pregnancy Test products

- 3.8 HPTs were the first pregnancy tests that did not need professional or laboratory input into the testing process and where the woman was the first to know the test results. They were marketed to doctors as a simple, reliable, quick and relatively inexpensive test.
- 3.9 Medicines are used to treat specific conditions, known as ‘indications’. During the 1960s most HPTs had at least two indications: pregnancy testing and secondary amenorrhea (lack of periods).¹²⁵ Some HPTs had additional indications, such as treating miscarriage.

Pregnancy test options 1950–1980

- 3.10 Pregnancy testing was very different in the 1950s to 1980s.¹²⁶ Before the 1950s pregnancy tests involved injecting a toad with urine (the Hogben or Toad test). If the woman was pregnant hormones in the urine would cause a breeding response in the toad. This was slow, costly and could only be carried out in specialist laboratories.
- 3.11 During the 1950s and early 1960s pregnancy tests were provided by the NHS, but only for women with a pressing medical need for a diagnosis. The Hogben (or Toad) test was carried out in some hospital pathology labs and by three centres in Edinburgh, Sheffield and Watford.
- 3.12 HPTs were used from 1950 onwards in the UK. If a woman was not pregnant a withdrawal bleed occurred up to a few days after taking the HPT.¹²⁷ In pregnant women any increase in hormones level due to the HPT was thought to add to the already high levels of natural hormones and so would not cause a withdrawal bleed.¹²⁸
- 3.13 From the mid-1960s immunoassays were used for pregnancy testing.¹²⁹ Early immunoassays tested urine or blood and were undertaken by doctors, chemists or

¹²⁵ Secondary amenorrhea is when a woman who has had at least one period, stops menstruating for three months or longer.

¹²⁶ A more detailed summary can be found in Annex E HPT Supporting Information.

¹²⁷ We are aware that some women did bleed after taking an HPT even though they were pregnant.

¹²⁸ See Higgins, GL and Sadler, WR ‘A two-tablet oral pregnancy test’ *Practitioner* 1960: **185**, 677-80.

¹²⁹ Immunoassays are tests that detect a specific protein by using an antibody to that protein. Pregnant women produce human chorionic gonadotrophin (hCG) and so an antibody to hCG can be used to test for pregnancy. Antibodies are very specially shaped proteins which fit to their target protein like a key in a lock.

in laboratories. In 1971 immunoassay-based home tests were first sold in the UK. These have been refined into the urine home test kits that are available today.

- 3.14 During 1966 pregnancy testing by the NHS and NHS reimbursement for HPTs¹³⁰ was investigated by the subcommittee¹³¹ on Pregnancy Diagnostic Tests.¹³² They asked external experts¹³³ about HPTs, who replied HPTs were potentially unreliable and it was suspected they caused abortions in pregnancies that were not well-established.
- 3.15 The subcommittee recommended replacing the Toad tests with immunoassays. Immunoassay components had to be refrigerated so these tests were carried out in hospital pathology laboratories. From 1967¹³⁴ GPs could send in samples for pregnancy testing for all women, not just those with pressing medical needs. The system was informed via a letter: *‘The Department now recommends that hospital authorities should arrange for pathology laboratories to accept requests for pregnancy tests on referral from general practitioners and should discuss the introduction of the new arrangements with Local Medical Committees. The requests could be met effectively by using immunological reagents.’*¹³⁵
- 3.16 These letters did not say HPTs should no longer be used as pregnancy tests despite the concerns over abortions. This was a significant moment. In our view, had doctors been informed not to use HPTs for pregnancy testing then fewer unborn children would have been exposed to them and the HPT narrative is likely to have been very different.

HPT usage

- 3.17 The number of women who used HPTs as pregnancy tests is uncertain.¹³⁶ This is difficult to establish because we don’t know how much HPT use was for pregnancy testing and how much was for other conditions like secondary amenorrhea. A compounding factor was the use of free samples of HPTs. These tablets were given, often from a doctor’s desk drawer, without a prescription and often with no record-keeping. For further detail, see Annex E HPT Supporting Information.

¹³⁰ Further detail is available in Annex E HPT Supporting Information.

¹³¹ A subcommittee of the DHSS’ Central Pathology Committee.

¹³² CSM, MH 149_1105. 1966

¹³³ Dr A. J. N Warrack, the Pathologist in charge of the Group Pathology Laboratory at the City General Hospital, Sheffield and Dr Bruce Hobson of the Department of Obstetrics and Gynaecology, University of Edinburgh.

¹³⁴ The documents in the files record two start dates, 1 January and 1 February. Other contemporaneous documents indicate that the services were not in place on 1 January, with letters sent in August.

¹³⁵ MH 149_1105 page 3 and Letter from Mrs E Croft, Ministry of Health Reference G/H118/01 dated 7 August 1967 to Secretaries, Regional Health Boards. MH159/78.

¹³⁶ See Annex 13 of the Expert Working Group Report, see FN 2.

The regulatory background – the impact of Thalidomide

- 3.18 Thalidomide triggered substantial, though by no means perfect, improvements in medicines regulation in the UK.¹³⁷ Between 1958 and 1961 Thalidomide was available on prescription in the UK. Thalidomide was a potent teratogen. It was often prescribed for morning sickness, and even a few tablets taken at a vulnerable stage in pregnancy could cause characteristic damage to limbs, eyes, ears, the heart and other organs.
- 3.19 After Thalidomide UK medicines regulation was overhauled. Initially a voluntary arrangement was made with the pharmaceutical industry. In 1964 the Committee on Safety of Drugs (CSD) was established. The CSD had no legal powers, it was purely advisory. Any CSD recommendations were upheld by agreement of the manufacturers. The CSD had subcommittees for Adverse Reactions (CSD/AR), Toxicity, and Clinical Trials.
- 3.20 The Medicines Act 1968 created a formal regulatory system. The CSD was replaced by the Committee on Safety of Medicines (CSM). The CSM could remove a product from the market or change its usage. A transition period to allow the pharmaceutical industry to adapt meant the 1968 Act only came into force on 1 September 1971.
- 3.21 Any medication known to be on the market immediately before 1 September 1971 could apply to the Medicines Division of the Department of Health and Social Security (DHSS) for an automatic licence, a Product Licence of Right (PLR).¹³⁸ There was no need to show safety or efficacy data to obtain a PLR, only to show that the product was on sale on 1 September 1971. Clearly this was unsatisfactory, so in October 1975 the Committee for the Review of Medicines (CRM) was created to review all PLRs by a final deadline of 20 May 1990.

The indication change for HPTs

- 3.22 In the 1960s the Joint Standing Committee on the Classification of Proprietary Preparations (MacGregor Committee) was the gatekeeper of NHS medicines sales. Its aim was ‘...*helping doctors to decide which should be used in the treatment of their patients.*’ The MacGregor Committee published the PropList and sent it to doctors. The PropList classified drugs into those the NHS should and should not use.

¹³⁷ More detail on the development of pharmaceutical and medical devices regulation can be found in Annex H History of Regulation.

¹³⁸ Medicines Act 1969, s 25-27.

- 3.23 In February 1970 the MacGregor Committee wrote to Schering that if the pregnancy test indication was deleted Primodos would be deemed acceptable for NHS prescribing.¹³⁹ In their letter the MacGregor committee wrote *'This matter has also been taken up with other manufacturers.'* However, the pregnancy testing indication remained on some non-Schering products. The file containing the relevant MacGregor Committee documents is missing. We do not know the relative importance of efficacy, safety concerns, financial considerations or other factors on their request for this change to the indication or which other manufacturers were involved, see Appendix 4 'How we Worked', paragraph 54.
- 3.24 Schering agreed to the deletion of the pregnancy test indication. It took some time for the Primodos package inserts to be updated. From September 1970 the Primodos package inserts did not include information on using Primodos to test for pregnancy.
- 3.25 The PropList informed doctors if a medicine was approved for NHS use, but there was often no information on what indications that medicine should be used for. The PropLists were cumulative. Products added as they were reviewed by the MacGregor Committee. However, the PropLists were incomplete as not all medicines had been assessed. The February 1970 PropList does not have an entry for Primodos and none of the HPT product entries in the 'Female Sex Hormones and Related Compounds' section contain any indications for use.¹⁴⁰ The June 1970 update to the PropList provided no new information on HPTs. It did not inform doctors about Primodos at all, nor about the indications for other HPTs. The June 1970 update was the last PropList published as later that year the MacGregor Committee was disbanded as part of reorganisations to implement the Medicines Act.
- 3.26 After the indication change the use of Primodos as a pregnancy test was 'off-label', meaning that a doctor took personal responsibility for that prescription and during any formal investigation such off-label prescribing might require special justification. Doctors were not directly notified of the indication change. They were expected to notice that the package inserts and/or the entries in the Monthly Index of Medical Specialties (MIMS) had changed. In August 1970 the Primodos indication in MIMS changed from *'secondary amenorrhea, early diagnosis of pregnancy'* to *'amenorrhea not due to pregnancy'*.

¹³⁹ Bayer's written evidence to the Review – Attachment 2.

¹⁴⁰ The products listed in the 'Female Sex Hormones and Related Compounds' section are: Amenorone, Amenorone Forte, Depo-Provera, Enavid 5mg, Enavid-E, Estrovis, Femipausin, Gonadotraphone L.H., Lynoral, Menstrogen, Methyltestosterone Sublings, Metrulen, Metrulen M, Norinyl-2, Norlestrin, Norlutin 'A', Orasecron, Ovestin, Pentovis, Perandren, Pregnyl, Provera, Secrosteron, Sustanon '100', Sustanon '250', TACE, TES P.P., Testoral Sublings, Vallestiril, TOVA.

Product Licences of Right (PLRs) for HPTs

- 3.27 In February 1971 Schering applied for a PLR for Primodos. The only recommended clinical use was for secondary amenorrhoea. The packaging leaflet section read: *‘Primodos is intended for the symptomatic treatment of secondary amenorrhoea of short duration not due to pregnancy, by the production of a withdrawal bleeding.’*¹⁴¹
- 3.28 Other manufacturers’ PLR applications included pregnancy testing.¹⁴² For example, in May 1972 in the PLR applications for Parolut tablets, Parolut Forte tablets and Parolut Forte Injections (produced by Wallace) listed *‘Secondary Amenorrhoea and Pregnancy Test’* as Recommended uses. The Medicines Division granted all these licences.
- 3.29 Roussel’s PLR application for Amenerone forte dated May 1972 listed the Recommended uses *‘As a pregnancy test and for recent cases of secondary Amenorrhoea.’*¹⁴³ This licence was granted. This is at odds with a letter from Dr Young of Roussel to Dr Inman, Senior Medical Officer of the Adverse Reactions subcommittee of the CSD, dated 3 September 1969 which says *‘...we ceased to promote Amenerone and Amenerone Forte in the United Kingdom several years ago and we have now removed pregnancy test as in indication.’*¹⁴⁴ On 27 November 1973 Roussel asked to vary the PLR to remove pregnancy testing.
- 3.30 In November 1974 the CSM/AR Subcommittee members seemed unaware that Amenerone forte and Primodos were no longer indicated as pregnancy tests.¹⁴⁵ Amenerone Forte and Primodos were the vast majority of the HPT market. In 1969 they had been directly informed by Roussel that the Amenerone Forte indication had been removed. Primodos had not been indicated as a pregnancy test since 1970.
- 3.31 Sales and prescription data show that usage of Schering and Roussel HPTs peaked in 1970 and dropped thereafter (see graph 3.1). It seems likely to us that had doctors been clearly informed of the indication change this decline would have been steeper.

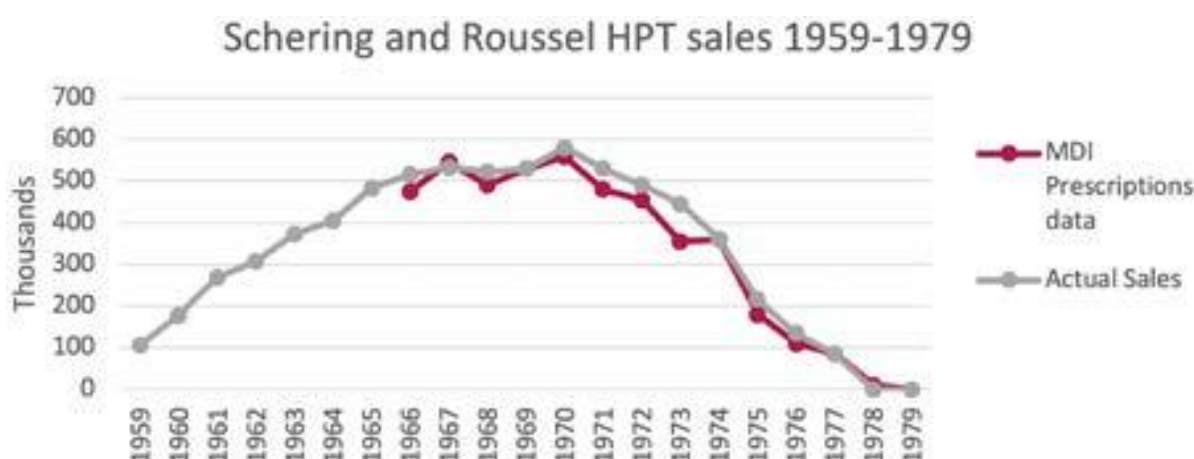
¹⁴¹ Bayer written evidence to the Review.

¹⁴² MHRA written evidence to the Review.

¹⁴³ *ibid.* The Amenerone PLR application did not include pregnancy testing.

¹⁴⁴ CSD/AR, MH 171_39 pages 58-59.

¹⁴⁵ The CSM Adverse Reactions Subcommittee Paper A from November 1974, National Archive files BN116_19 Page 17 and MH 171_61 available at <https://mhra-gov.filecamp.com/s/BBx98TuW8gFN2IZ/fo>



Graph 3.1 Sales of Schering and Roussel HPT products 1959 to 1978¹⁴⁶

Concerns raised – Responses to HPT associated malformations, miscarriages & deaths

- 3.32 In 1978 the ACDHPT was set up. Their concerns were that HPT use in pregnancy caused malformations (sometimes so severe that the baby died) and miscarriages. Another concern was that some doctors and some women believed HPTs could be used for deliberate abortions, making them inherently unsuitable as pregnancy tests.
- 3.33 Papers have reported associations with a wide range of malformations after HPT use including nervous system defects; congenital heart defects; orofacial clefts; digestive system and abdominal wall defects; urinary system defects; non-virilisation genital defects; musculoskeletal defects (including limb reductions); and VACTERL syndrome.¹⁴⁷
- 3.34 There have also been concerns that HPT use was linked to miscarriages. The 2017 EWG report states *‘there was no evidence that administration of these hormones at the licensed doses used in Primodos during early pregnancy were associated with an increased risk of miscarriage.’*¹⁴⁸ Our terms of reference meant that we did not consider the scientific evidence on HPT use and miscarriage. We did however consider how any such evidence was used by the regulators and manufacturers to assess HPT safety.

¹⁴⁶ Data from Dr Wiseman’s Report available at Annex 13 of the EWG Report. MDI data is unavailable pre-1966.

¹⁴⁷ VACTERL – Vertebral defects, Anal atresia, Cardiac defects, Trachea-Esophageal fistula, Renal anomalies, and Limb abnormalities.

¹⁴⁸ EWG report Section 6.4, page 84, FN 2.

- 3.35 Similarly, the scientific evidence on use of HPTs aiming to trigger an abortion was also not within our terms of reference.¹⁴⁹ We did however consider how the regulators and manufacturers used any knowledge they had of the use of HPTs with this aim.

HPTs and malformations

- 3.36 From the 1920s onwards animal experiments had demonstrated that exposing fetuses to hormones could cause genital abnormalities. For many decades medicines containing hormones have been used to support pregnancies at risk of miscarriage. From the mid-1950s it was widely perceived that girls exposed to such hormones in the womb were at risk of virilisation, that is the development of male physical characteristics. The doses and timing of hormones used to support pregnancy differ from HPTs; HPTs were a short exposure; pregnancy support requires a sustained dosage.
- 3.37 Hormones are still used to support pregnancies. Recent studies have shown that the type of hormones that are currently used to support pregnancies do not affect miscarriage rates and do not lead to increased virilisation or malformation rates.¹⁵⁰ In her oral evidence Professor Lesley Regan,¹⁵¹ an author on the PROMISE trial, said, *‘The progestogen that was used in the PROMISE trial is a different generation of progestogens but I think it was – we recruited a thousand women to that trial over seven different centres. It was a pretty extensive – pretty expansive cohort. I think if there had been meaningful abnormalities because of progestogen challenge to the foetus we would have seen it.’*
- 3.38 A 1958 paper on malformations in Scotland suggested that HPTs might result in non-genital malformations, but no data was supplied with this claim.¹⁵² A 1964 publication by Dr Smithells, a well-respected expert in this field, suggested that HPTs were probably not harmful to babies based on unpublished data he had.¹⁵³ This Smithells paper was shared with the CSD/AR prior to publication.

¹⁴⁹ This issue is further detailed in Annex E HPT Supporting Information.

¹⁵⁰ PROMISE trial Coomarasamy A, et al *Health Technol Assess* 2016;20(41) <https://doi.org/10.3310/hta20410>

¹⁵¹ OH RCOG 7th February 2019.

¹⁵² Edwards, J. H. (1958) Congenital Malformations of the Central Nervous System in Scotland. *Br J Prev Soc Med* 12(3): 115-130.

¹⁵³ Smithells, R. W. (1964). *Drugs and Foetal Development*. *Prescribers' Journal* 4(2): 21-23. The data referenced in this paper does not seem to have been published

- 3.39 In 1967 Isabel Gal and colleagues published preliminary findings comparing HPT use in 100 mothers of babies with neural tube defects¹⁵⁴ and 100 mothers of healthy babies.¹⁵⁵ This was the first statistically significant association between HPT use and malformations. Concerns were raised and requests for further funding were made to the Medical Research Council as it looked *‘as if it could be another thalidomide story.’*¹⁵⁶
- 3.40 The 1967 Gal et al paper was shared with the CSD before publication. The CSD/AR discussed the methodology and the interpretation of the results. Dr Gal was asked to clarify some points. The CSD/AR sought expert advice from Prof. Jeffcoate (Professor of Obstetrics and Gynaecology, the University of Liverpool), Dr Smithells (Consultant Paediatrician at Alder Hey Hospital and holder of the Liverpool Congenital Abnormalities Register), and the Royal College of General Practitioners (RCGP) on their Outcomes of Pregnancy Survey.
- 3.41 The CSD/AR acknowledged that Gal and colleagues had produced *‘prima facie evidence that these fetal abnormalities may be drug induced’*,¹⁵⁷ but they thought there were substantial flaws in the paper. Dr Inman of the CSD/AR wrote *‘The Carshalton workers drew their affected children and controls from different catchment areas, and this to my mind invalidates their work.’* There were well-documented differences between the control and HPT groups in Dr Gal’s study.¹⁵⁸
- 3.42 A 1967 CSD press release¹⁵⁹ states, *‘The Committee have been informed of the results that have been obtained at Carshalton and have sought expert opinion. The consensus of that expert opinion is that there is no scientific evidence to support the view that the hormones used in pregnancy tests can cause congenital malformations. The report was a preliminary one. Further work is required to determine whether the drugs are completely safe. At the moment the committee can find no evidence to support the view that a general warning is necessary.’*
- 3.43 This must be taken in context. In 1967 just one publication showed a significant link between HPT use and malformations. At this time the link was tenuous.

¹⁵⁴ The Gal paper featured babies with hydrocephalus (water on the brain) or meningomyelocele (where part of the brain or spinal cord is exposed through an opening in the spine, which can cause partial or total paralysis below that point).

¹⁵⁵ Gal, I., B. Kirman, and J.A.N. Stern, *Hormonal Pregnancy Tests and Congenital Malformation*. Nature, 1967. **216**: p. 83. <https://doi.org/10.1038/216083a0>

¹⁵⁶ Quote from a letter from Dr Richter to Dr Herrald dated 23 June 1967, FD 23_127 page 6.

¹⁵⁷ CSD/AR MH 171_39, (p19).

¹⁵⁸ The affected mothers were selected from all around the south of England; in contrast control mothers came from Kingston Hospital, Surrey see Laurence, M et al. ‘Hormonal Pregnancy Tests and Neural Tube Malformations’ Nature 1971: **233**, 495.

¹⁵⁹ We have not been able to locate the original press, it is referenced in correspondence CSD/AR MH 171_67 Page 30.

Dr Inman wrote in his autobiography, *'Had we been convinced by Dr. Gal's study the Committee would have banned HPTs immediately in 1967.'*¹⁶⁰ Even under today's rigorous EU-wide drug labelling a warning would not be added to drug leaflets unless a causal relationship with the adverse events is at least a reasonable possibility based on the facts. The CSD investigated, consulted experts and concluded there was not a causal link. The CSD was set up in the wake of the thalidomide tragedy, so it would have been expected that they would be particularly sensitive to potential teratogenicity. Had they adopted a more cautious approach the many thousands of women who took these tablets as a pregnancy test might have been prevented from doing so, resulting in fewer pregnancies being exposed and hundreds of women being spared from the anxiety and guilt that resulted.

- 3.44 Given the concerns raised, the non-essential nature of HPTs and the provision of risk-free alternative tests, we consider that the CSD focus should not have been whether or not to issue a warning. **They should have recommended the withdrawal of the indication for use as a pregnancy test in 1967.** This was the same year that DHSS had recommended that hospitals accepted pregnancy tests from GPs, so there was an alternative means of pregnancy testing.
- 3.45 This chimes with contemporaneous thinking. In his 1964 paper, which the CSD/AR had read, Dr Smithells wrote *'...if there are reasonable grounds for suspecting that a drug may be teratogenic, its use in early pregnancy must be stopped. It would be morally indefensible to put the suspicion to the test and the problem must remain unsolved.'*
- 3.46 The CSD minutes do not record a risk-benefit analysis for HPTs, but Dr Inman wrote to Dr Gal,¹⁶¹ *'My personal view about the value of pregnancy tests is identical to yours, I frankly do not think that they are sufficiently useful when compared with other biological methods to justify even the slightest risk of teratogenicity.'*
- 3.47 In his autobiography Dr Inman writes, *'but there was another aspect that had to be absolutely taboo. Most of the hormones that could be used for the pregnancy test also had important applications in the treatment of various gynaecological disturbances. Even more important, the HPT hormones were also very similar to the hormone mixtures used for contraception. A thalidomide-type scare in the media could easily cause panic among women using oral contraceptives.'*
- 3.48 In 1967 Schering UK commissioned expert statistical analysis from Dr Denis Cooke on HPTs and malformation rates: *'...he compared the increase in the sales of*

¹⁶⁰ Bill Inman 'Don't tell the patient: Behind the drug safety net' Highland Park 1999.

¹⁶¹ MH 171_39 Page 42.

*primodos with the number of recorded deformities in newborns, which, he says, “show a rather alarming direct and strong correlation.”*¹⁶² These findings were independent of Dr Gal’s findings.

- 3.49 The views expressed in contemporaneous correspondence from Schering Germany indicate that they did not regard the evidence available as indicating a causal link between HPT use and malformations and they saw no reason to withdraw Primodos. A more precautionary attitude was expressed by Schering UK in a letter of 6 June 1968 to Schering Germany *‘It is our moral duty as a manufacturer to do all we can to ensure the non-hazardousness of the preparations we have on the market. Where a suspicion of this kind has been raised by a researcher, whose integrity and ability can hardly be questioned, the burden of proof must lie with us. It is incumbent upon us to show that the preparation is safe to use, and that it is not the role of outsiders to prove that it is not. Medicolegal, we would get into difficulties, both as a company and as individuals responsible for the development and sale of Primodos, if an association between the anomalies of CNS and our preparation were to be demonstrated. From an ethical point of view, we are not satisfied with what has been done to remove the suspicion which has fallen upon us. Not enough has happened that we can continue to confidently promote the fact that Primodos for pregnant women is available here.’*¹⁶³ A year later, on 22 July 1969, Schering UK wrote to Schering Germany and recommended removing the pregnancy testing indication.¹⁶⁴ Despite these concerns, the way Primodos was marketed in the UK was not altered. Given the association detected by Dr Cooke’s analysis was independent of the association that Dr Gal reported, we agree with Schering UK’s stance that action should have been taken.
- 3.50 It does need to be recognised that the pharmaceutical regulatory system was in its infancy at this time and was nowhere near as comprehensive as it needed to be. The CSD was advisory, it had no powers and any changes only happened because manufacturers cooperated.¹⁶⁵ Dr Inman is reported to have said the CSD was not *‘happy’*¹⁶⁶ about HPTs. In a letter to Schering UK in early 1969 he wrote *‘You say that your company is actively pursuing the question of whether or not Primodos should*

¹⁶² HC Deb (23 October 2014) Vol 586, Col 1118 Available at <https://hansard.parliament.uk/Commons/2014-10-23/debates/14102384000001/OralHormonePregnancyTests>

¹⁶³ LandesArchiv 13198 (trans) Memorandum from Amon with a summary of Primodos pages 9-10.

¹⁶⁴ LandesArchiv 13198 (trans) Memorandum from Amon with a summary of Primodos page 13.

¹⁶⁵ For more detail on the relationships between the CSD and the pharmaceutical industry see examples from John Griffin *Chapter 17 History of drug regulation in the UK* in John Griffin *The textbook of pharmaceutical medicine 6th Edition*, (2009, Wiley Blackwell & BMJ Books) John Abraham (1997) *The science and politics of medicines regulation*. Sociology of Health and Illness, 19 (19B). pp. 153-182. ISSN 0141-9889.

¹⁶⁶ LandesArchiv 13198 (trans) Memorandum from Amon with a summary of Primodos pages 10.

*be withdrawn from the market. Personally my view is that the data you have so far are quite unhelpful in reaching this decision.*¹⁶⁷.

- 3.51 In our view the 1960s regulatory system had a clear and obvious flaw. Withdrawal decisions were made by manufacturers who had a financial interest in the product remaining on the market. This was wrong and was rectified by the Medicines Act 1968.
- 3.52 HPTs had not been exonerated, a suspicion remained. Dr Inman wrote that although he was unconvinced about the validity of Gal's data, *'I do not think we can rule out the possibility altogether.'*¹⁶⁸ A proposed CSD research study was expanded to investigate HPTs and the CSD and manufacturers agreed that the distribution of free samples of HPTs to doctors would stop.¹⁶⁹
- 3.53 Dr Inman kept in contact with Dr Gal, and during 1969 she shared information on HPTs and malformations that she had obtained from the RCGP and Schering. Dr Inman found these disturbing. In response he obtained further data from the manufacturers and the RCGP. By November he wrote *'...these did not produce any concrete results and it is somewhat difficult to summon up enough enthusiasm to place a high priority on this when so much other and possibly more important work is pressing.'*¹⁷⁰

CSD/CSM Maternal Drug Histories and Congenital Malformations study – initial results

- 3.54 In late 1968 the CSD and the Registrar General's Office planned a study on drugs in pregnancy. It began in 1969 looking at three aspects: antiepileptics and cleft palates; antihistamines and limb reductions; HPTs and spina bifida. It subsequently included other malformations and was published as Greenberg et al 1975 and 1977.
- 3.55 In June 1970 preliminary results of this study showed eight of the 87 babies with abnormalities had been exposed to hormones compared to two of the controls. In retrospect Dr Inman wrote, *'Thus at this stage there was a suggestion that Dr. Gal might be correct but the matter was by no means settled.'*¹⁷¹

¹⁶⁷ MH 171_64. Page 77.

¹⁶⁸ MH 171_39 page 24.

¹⁶⁹ The agreement not to give out more samples of HPTs to GPs does not mean that GPs stopped handing out any HPT samples they already had. The 2017 EWG report (see FN5) states that 'the number of samples of Primodos distributed by Schering are said to have fallen from 25,539 to 150 during the period 1966–1968.'

¹⁷⁰ CSD/AR MH171_39 page 61.

¹⁷¹ MH 171/67 page 50.

- 3.56 In May 1973 Dr Inman reported an excess of HPT exposure in babies with cleft palates and with other abnormalities. *‘In both groups there is an apparent excess of use of hormonal pregnancy tests. This supports the suspicion that we already had when we designed the study, though our original suspicions were based on an alleged increase in the incidence of spina bifida and hydrocephalus in babies.’*¹⁷² The malformations reported after HPT use were not limited to neural tube issues.
- 3.57 The CSD has been criticised as being unwilling to act until they were certain of a causal link between a drug and an adverse event.¹⁷³ However, HPTs were non-essential with a risk-free alternative, and their own preliminary results indicated an association with higher malformation rates, yet the CSD/CSM took no action. We maintain that exposing unborn babies to any alleged risk was unacceptable in these circumstances.
- 3.58 Early in 1973 papers came out reporting a statistically significant link between HPT use and other malformations; VACTREL¹⁷⁴ and congenital heart defects,¹⁷⁵ followed in July by a paper linking HPTs and limb reductions.¹⁷⁶
- 3.59 However, two further publications in 1973 questioned the validity of a link between HPT use and neural tube defects.¹⁷⁷ Oakley et al wrote that their findings from a large group study *‘...leave little reason, now, to think that hormonal pregnancy tests cause neural-tube malformations.’*
- 3.60 In November 1974 two papers by Dr Inman detailing interim results of the Maternal Drug Histories study were presented to the AR subcommittee.¹⁷⁸ Paper B is the preliminary analysis. 136 affected babies and 149 matched controls were studied. 23 affected babies had been exposed to a hormone pregnancy test, compared to 9 controls. This was a statistically significant difference.
- 3.61 Paper A, a synopsis, states, *‘If this finding is confirmed the actual number of babies who may have been affected by the hormonal pregnancy test could be quite large...*

¹⁷² MH 171_67 page 52.

¹⁷³ For example see the assessment of CSM’s role in the Practolol disaster in John Abraham & Courtney Davis, ‘Testing Times: The Emergence of the Practolol Disaster and its Challenge to British Drug Regulation in the Modern Period’ *Social History of Medicine* 2006: 19(1): 127–147 <https://doi.org/10.1093/shm/hkj005>

¹⁷⁴ Nora, J and Nora, A ‘Birth defects and oral contraceptives’ *The Lancet*, 1973. **301**(7809), 941-942.

¹⁷⁵ Levy, E et al. ‘Hormone treatment during pregnancy and congenital heart defects’ *The Lancet* 1973: **301**(7803), 611 [https://doi.org/10.1016/s0140-6736\(73\)91398-6](https://doi.org/10.1016/s0140-6736(73)91398-6)

¹⁷⁶ Janerich, DT, Piper, JM and Glebatis, DM ‘Hormones and limb-reduction deformities’ *The Lancet*, 1973: **2**(7820), 96-7 [https://doi.org/10.1016/s0140-6736\(73\)93293-5](https://doi.org/10.1016/s0140-6736(73)93293-5)

¹⁷⁷ Oakley, GP, Flynt, JW, Falek, A ‘Hormonal pregnancy tests and congenital malformations’ *The Lancet* 1973 [https://doi.org/10.1016/s0140-6736\(73\)93154-1](https://doi.org/10.1016/s0140-6736(73)93154-1) : **2**(7823), 256-7; Sever, LE ‘Hormonal Pregnancy Tests and Spina Bifida’ *Nature* 1973: **242**, 410 <https://doi.org/10.1038/242410a0>

¹⁷⁸ BN116_19 Page 17 and MH 171_6 page 1.

... Since alternative pregnancy tests are available and other published evidence supports the same hypothesis the Committee may wish to consider whether or not the manufacturers of hormonal pregnancy tests should be put in the picture at this stage of the study. Most of the products on the market are used for other purposes both by pregnant and non-pregnant women, and if the Committee agree that action should be considered, it could take the form of a discrete withdrawal of one indication for the use of these drugs rather than a recommendation that the product licences should be withdrawn absolutely.’ The AR subcommittee appear unaware that the pregnancy testing indications for the market leading products had been withdrawn in or before 1970. The first instinct was to discretely contact manufacturers. Warnings to doctors or patients are not mentioned.

- 3.62 At their meeting on 28 November 1974 the main Committee disagreed with the AR subcommittee plans. The CSM *‘...considered that in view of the possibility of leakage of information, combined with the advice that the study ought to be completed within six months, no approach should be made to the manufacturers at this stage.’*¹⁷⁹
- 3.63 The Adverse Reactions subcommittee were concerned about this. Minutes of the January meeting reveal *‘Members expressed concern that the Main Committee had decided not to approach the manufacturers of hormonal pregnancy kits at this stage (Minute 3.5 refers), and were concerned that criticism could be levelled against the Committee if they failed to give early warning of an apparent hazard merely to enable a study to be prepared for publication. They therefore endorsed the recommendation made at the last meeting that an early approach should be made to these manufacturers in order than they might be forewarned in case they wished to take any actions.’*¹⁸⁰ As endorsed by the AR subcommittee Dr Inman approached Schering in January 1975. The minutes indicate this was not sanctioned by the main CSM committee.
- 3.64 This approach to Schering was recorded in an internal Schering memo dated 22 January 1975 which records, *‘Dr Esche has informed us that Dr Pitchford from England has heard from Mr Inman of the Committee on Drug Safety, that hormonal combinations for pregnancy diagnosis are considered to lead to an increased rate of malformations. The quote is thought to be 5:1 in favour of non-applications of these preparations. Thus, DUOGYNON [Primodos] will not be used for pregnancy testing in England any longer.’*¹⁸¹

¹⁷⁹ CSM BN116_5 (p5).

¹⁸⁰ CSM/AR BN116_19 Page 17.

¹⁸¹ LandesArchiv 13222 (translation) page 29 *‘Schering memo dated 22.01.75’*.

- 3.65 Media interest in HPTs was building. An LWT programme broadcast on 16 April 1975, and a Times article the next day criticised the CSD/CSM and industry inaction over HPTs.
- 3.66 In April preliminary CSM/OPCS¹⁸² results were published as Greenberg et al 1975,¹⁸³ and conclude, *‘This evidence supports the recommendation given in your article that “There is little justification for the continued use of withdrawal-type pregnancy tests when alternative methods are available.”’*

The first CSM warning in 1975 and its aftermath

- 3.67 By this date various international regulators had acted to stop the use of hormonal preparations as pregnancy tests. Issuing a warning to doctors was discussed at the main CSM meeting on 21 May 1975.¹⁸⁴ *‘Sir Eric [CSM chair] was concerned about possible legal implications in that if there were an association known to the Committee then there may be a legal obligation to warn physicians as soon as possible. The Department’s legal advisor thought that this was a matter which could cause difficulty in the future.’* The minutes record a reluctance to issue a warning, *‘Sir Eric’s view was that the CSM was reluctant to publish a warning before full information was available, but the action of the other drug regulatory authorities may put them into the position of having to do so.’*¹⁸⁵
- 3.68 The final outcome of the discussions was that *‘The Sub-Committee agreed to the suggestion that a leaflet in the Adverse Reactions Series should be published, but emphasised that it should be made clear that the Committee were unable to give a final decision and that the leaflet should avoid telling prescribers what to do.’*¹⁸⁶
- 3.69 The CSM issued a warning on a possible association between HPTs and congenital abnormalities on 5 June 1975.¹⁸⁷ *‘The Committee of Safety of Medicines have sent to all doctors in the United Kingdom a letter informing them of a possible association between hormonal pregnancy tests and an increased incidence of congenital abnormalities. They recommend that, in view of the possible hazard, doctors should not normally prescribe certain hormonal preparations for pregnancy tests.’*¹⁸⁸

¹⁸² The Registrar General’s Office had been renamed to the Office of Populations Censuses and Surveys (OPCS).

¹⁸³ Greenberg, G., et al., Letter: Hormonal pregnancy tests and congenital malformations. Br Med J, 1975. 2(5964): p. 191-2.

¹⁸⁴ CSM/AR BN116_19 page 4.

¹⁸⁵ *ibid.*

¹⁸⁶ *ibid.*

¹⁸⁷ CSM Adverse Reaction Series No 13.

¹⁸⁸ CSM Adverse Reaction Series No 13.

- 3.70 On the day the warning was issued Schering UK wrote to MIMS requesting the following addition to the Primodos entry ‘*Contraindication – Pregnancy*’.¹⁸⁹ The editor at MIMS replied that as the indication specifically excluded pregnancy it was not necessary to add a contraindication. Schering repeated their request and as a result the indication that appeared in MIMS in August 1975 read ‘*Secondary Amenorrhea of short duration, where pregnancy has been excluded*’.¹⁹⁰
- 3.71 A Schering memo from 1977 states that at the start of June 1975 Schering wrote a Dear Dr letter, ‘*which stated that retrospective epidemiological studies had given rise to a suspicion that Primodos should not be used if pregnancy could not be excluded. Pregnancy had now been included as a contraindication in the product accompanying literature*’ and that Roussel had also sent out a Dear Dr letter in July 1975.¹⁹¹
- 3.72 After the warning Dr Gal wrote to the CSM and to Dr Inman several times expressing her dissatisfaction at their handling of HPTs. On 8 July 1975 Dr Inman replied ‘*We have been informed that none of the manufacturers was promoting these mixtures as pregnancy tests, and only comparatively recently discovered that some doctors were persisting in using them. Because of this we published a preliminary communication, although our scientific instincts were against this. The Committee felt that we had a duty to publish this warning even though the case was not proven*’.¹⁹² He writes that they were unaware of ongoing use of HPTs. In 1970, 1973 and 1974 the Adverse Reactions Subcommittee were shown preliminary results from their own study, which clearly showed pregnant women were using HPTs and that HPT use was linked to higher rates of malformations.
- 3.73 On 4 August 1975 Dr Gal sent a critique of the CSD/CSM to Sir Eric Scowen [the CSM Chair]. ‘*By downplaying the significance of the original observation (as attempted in yours and in Dr. Inman’s letters, and as stated in the official press communique and in the article in the “Sunday Times” on 8th June) the Committee’s responsibility is not averted from allowing the 8 years use of an unnecessary diagnostic test table, whose serious irreversible adverse effects were well known to them. It is also of interest that the warning on the hormonal pregnancy test was introduced earlier in the United States, Australia and Ireland than here, despite the fact that the concept originated in this country, and the Committee was in the favourable position of having first-hand knowledge of it in 1967. Although the Committee’s own study*

¹⁸⁹ Bayer written evidence.

¹⁹⁰ MIMS August 1975.

¹⁹¹ LandesArchiv 13198 (trans) page 19.

¹⁹² MH 171_67 Page 33/34.

confirmed my observation (BMJ. 28 Apr.1975), active steps were only taken on 5th June, due to pressure of the public press ("Sunday Times" 25 May).'¹⁹³

- 3.74 We agree with Dr Gal's statement that HPTs were unnecessary. As we have noted above, we are of the view that their use as pregnancy tests should have been stopped in 1967 due to the suggestion of increased risk. We also consider that further opportunities for action were missed in 1970, 1973 and 1974 when the preliminary results from the CSD/CSM study, which indicated an association between HPT use and malformations, became known to the CSD/CSM.
- 3.75 Internally Dr Inman acknowledged the CSD shortcomings.¹⁹⁴ *'The Department would be vulnerable if Dr. Gal launched an attack on the Committee by drawing attention to the eight years that elapsed from the time she published her observations to the time we were in a position to publish a preliminary communication based on our own work. She is aware that the pilot stage of our study commenced in 1969 and it must be obvious to her, from the small number of cases assembled in our preliminary communication, that progress has been extremely slow. It may not have escaped her notice that, if the relative risk suggested by our publication turned out to be true, a large number of congenitally abnormal babies have been born as a result of hormonal pregnancy tests carried out after publication of her paper.'*
- 3.76 Dr Inman subsequently met Dr Gal and then wrote to her¹⁹⁵ *'...the question of the eight year gap between your publication and ours. The answer to the latter, is, quite simply, that the facilities for a more rapid assessment of the problem simply were not available.'* Dr Inman described the CSD drugs in pregnancy study as *'lamentably slow, largely because higher priority had been given to concurrent problems with oral contraceptives, asthma deaths, the Eraldin disaster and the lack of equipment and staff.'*¹⁹⁶
- 3.77 An internal memo by Dr Inman described the meeting. *'...she feels she has strong grounds for attacking the Committee about the eight year gap between her paper and the appearance of the preliminary communication in the British Medical Journal based on the Committee's study. She feels she should have been given an opportunity to discuss our results with her before publication, and that the letter in the BMJ should have acknowledged her personally as the discoverer of the teratogenic potential of hormonal pregnancy tests, that the Committee probably would not have initiated the study had she not first drawn attention to the hazard and that a large number of abnormal babies may have been born during the eight*

¹⁹³ MH 171_ 67 Page 39.

¹⁹⁴ MH 171_ 67 (p46-8).

¹⁹⁵ MH 171_67 (p73).

¹⁹⁶ Bill Inman 'Don't tell the patient: Behind the drug safety net' Highland Park 1999 (p119).

*years that have elapsed. Most of these criticisms had been answered in early correspondence with her, but of course we are defenceless in the matter of the eight-year delay.'*¹⁹⁷

- 3.78 In the three years after the first CSM warning in 1975 some papers were published which found a statistically significant association between in utero exposure to hormones and cardiovascular anomalies.¹⁹⁸ Other studies did not detect an association between hormone exposure and cardiac defects.¹⁹⁹ Other malformations including skeletal²⁰⁰ and limb reductions²⁰¹ were investigated but no significant link was found.

CSD/CSM Maternal Drug Histories and Congenital Malformations study – final results

- 3.79 On 1 October 1977 the full CSD/CSM study results were published as Greenberg et al. They analysed neural tube defects, oral clefts, limb malformations and other abnormalities. They reported a significant difference between case and control use of HPTs even if families with a history of congenital abnormalities were excluded. They concluded *'The excess use of HPT by case mothers found by us was not great and the association with malformations nonspecific; alternative risk-free methods of pregnancy diagnosis are, however, available and the use of HPTs is unnecessary.'*²⁰²
- 3.80 Ongoing HPT use was raised in the medical press after the CSM study was published. On 14 October 1977 Schering wrote to GPs and gynaecologists reminding them of the 1975 CSM warning and contraindication of Primodos in pregnancy.²⁰³
- 3.81 On 25 October 1977 CSM phoned Dr Wiseman of Schering for information, he wrote back that day *'total prescriptions for Primodos from July '76 to June '77 were 55,000; it appears that 9.3% of these prescriptions being used as*

¹⁹⁷ MH 171_67 (p74).

¹⁹⁸ Heinonen, OP et al. 'Cardiovascular birth defects and antenatal exposure to female sex hormones' New England Journal of Medicine 1977: **296**(2), 67-70 <https://doi.org/10.1056/NEJM197701132960202>; Janerich, DT et al. 'Congenital heart disease and prenatal exposure to exogenous sex hormones' British Medical Journal 1977: **1**(6068), 1058-60 <https://doi.org/10.1136/bmj.1.6068.1058>

¹⁹⁹ Goujard, J and Rumeau-Rouquette, C 'First-trimester exposure to progestagen/oestrogen and congenital malformations' The Lancet 1977: **1**(8009), 482-3 [https://doi.org/10.1016/s0140-6736\(77\)91966-3](https://doi.org/10.1016/s0140-6736(77)91966-3)

²⁰⁰ *ibid.*

²⁰¹ Smith, ES, et al. 'An epidemiological study of congenital reduction deformities of the limbs' British Journal of Preventive and Social Medicine 1977: **31**(1), 39-41 <https://dx.doi.org/10.1136%2Fjech.31.1.39>

²⁰² Greenberg, G., et al., *Maternal drug histories and congenital abnormalities*. Br Med J, 1977. **2**(6091): p. 853-6.

²⁰³ BN116_24 (p6).

pregnancy tests' and enclosing a copy of the above Dear Doctor letter and the Primodos datasheet.²⁰⁴

- 3.82 On the basis of the evidence we have seen in the National Archive files, the telephone call from CSM to Schering (detailed above) was the first time any regulatory agency had asked if HPTs were still being used as pregnancy tests. The indication had changed in 1970.
- 3.83 In the two years following the 1975 CSM warning HPTs were still being used as pregnancy tests. The 1975 CSM warning had not been sufficiently effective.

The second CSM warning in 1977 and its aftermath

- 3.84 The continuing use of HPTs was raised by the Chairman at the CSM meeting on 27 October 1977.²⁰⁵ *'...he considered that it would be advisable for the Committee to send a further warning leaflet to doctors, reminding them of the possible hazards and drawing attention to the recent published article by Greenberg et al.'* This suggestion was met with some resistance. *'The question of whether the Committee's warning leaflet should be used for such reminders or whether they should be reserved for new dangers was raised.'*²⁰⁶ However, they agreed to issue a warning.
- 3.85 On 17 November 1977 a CSM second warning 'HORMONAL PREGNANCY TESTS AND CONGENITAL ABNORMALITIES: A further statement' was sent to all doctors, hospital and retail pharmacists.²⁰⁷ *'In June 1975 the Committee on Safety of Medicines published a warning about a possible association between Hormonal Pregnancy Tests and Congenital abnormalities (Adverse Reactions Series No. 13) The publication was based on preliminary evidence: further results have now been published (Greenberg, et al British Medical Journal 1977, 2, 853-856) and the association is confirmed. The Committee therefore reiterate their view, expressed in their earlier warning (which is attached) that hormonal tests for pregnancy should not be used.'*

²⁰⁴ BN116_24 Page 5.

²⁰⁵ BN116_9 page 12.

²⁰⁶ *ibid.*

²⁰⁷ CSM Adverse Reaction Series No 16.

Alternative methods are available which are free from this risk.

Most of the preparations referred to in the earlier leaflet were removed from the market. The data sheets for those which remain for other indications state clearly that pregnancy is a contraindication for their use.'

The withdrawal of Primodos in the UK and worldwide

- 3.86 On 25 January 1978 Schering asked the DHSS to end their HPT licences due to falling sales. On 14 February Schering withdrew the pregnancy test indication worldwide.²⁰⁸

Pressure for a public inquiry

- 3.87 In February 1978 Jack Ashley MP met parents of children with damage believed to be due to HPTs, and the ACDHPT was formed. Mr Ashley subsequently asked questions in Parliament about the numbers of babies exposed, ADR reports, actions taken, and a public inquiry.
- 3.88 On 26 May 1978 Mr Ashley asked the Secretary of State whether he accepted that studies demonstrated that HPTs often caused abnormalities. Roland Moyle MP, the Minister of State, replied: *'Until today my answer to that question might have been "Yes". However, today I have been able to get some evidence of testing in this field by the German Research Association of the 7,870 women covered in the preliminary report, 337 had used hormonal pregnancy test drugs. In a group of this size it would be expected that there would be 5.4 major abnormalities in the births to these women. In fact, it turned out that there were six. There would have been expected to be 74.8 minor abnormalities in babies born to a group of women of this number. In fact, there were 76. Therefore, it is difficult to connect that piece of evidence with the case that hormonal pregnancy testing damages the foetus.'*²⁰⁹
- 3.89 These figures were sent to Dr Inman by Prof Koller²¹⁰ and are different from the figures Schering had.²¹¹ However, neither set of figures show a statistically significant difference in overall malformation rates between HPT users and controls.

²⁰⁸ Bayer written evidence.

²⁰⁹ HC Deb (26 May 1978) Vol 950, Col 2006 Available at <https://hansard.parliament.uk/Commons/1978-05-26/debates/fb0cdabe-f6e0-4f49-b8f3-27f232f31c4b/CommonsChamber>

²¹⁰ Dr Inman's figures came from Prof Koller. See page 121 of Bill Inman 'Don't tell the patient: Behind the drug safety net' Highland Park 1999 and Landesarchiv file 13190 (translation) page 103.

²¹¹ LandesArchiv 13198 (translation) page 64 'Report on talks with Dr. Inman on the end of the Bermuda Symposium on 7 and 8 April 1978'; LandesArchiv 13918 (original) pages 182-183.

- 3.90 Dr Gal sent Mr Moyle a report on 21 July 1978.²¹² It reviewed the literature on HPTs and other hormones used during pregnancy and malformations. She asserted that HPTs caused malformations and that the CSD/CSM warning was unacceptably slow.
- 3.91 Dr Gal's report was sent to the Adverse Reactions Subcommittee. The main CSM minutes from September read *'The Chairman explained that the Minister, to whom Dr Gal's report was addressed, would require a reasoned reply answering the points which she raised'*.²¹³
- 3.92 Five points were supplied to the Minister regarding Dr Gal's report: her papers were scientifically unsatisfactory (wrong controls; HPT timing issues); her review looked at exposure to all hormones not just HPTs; in the two large prospective studies HPTs did not increase malformations; only the Gal and Greenberg papers found a statistically significant rise in malformations after HPT use. Gal's study was scientifically unacceptable. Greenberg et al was intended to detect signals not causality and the small additional risk was likely due to an unidentified bias; and, HPT users were not typical of all women who became pregnant. For example, 18 of the 22 of Dr Gal's HPT users had asked for an abortion.

The Primodos litigation

- 3.93 In 1977 the ACDHPT started litigation against Schering for negligence. Concerns over Dr Inman of CSM's role in this litigation have been raised.²¹⁴ A Schering memo of a symposium held in Bermuda in April 1978²¹⁵ reports a conversation with Dr Inman, *'...he has destroyed all the material on which his investigation is based, or made it unrecognizable, which makes it impossible to trace the individual cases taken into the investigation. I understood Dr. Inman that he did this to prevent individual claims from using this material.'* This is consistent with the approach that Dr Inman describes in relation to an earlier unrelated subpoena.²¹⁶

²¹² Gal I Teratological adverse drug effects: Review of evidence implicating hormonal pregnancy tests. available at <https://mhra-gov.filecamp.com/s/GZdoZEG9hoT4o6nZ/fo>

²¹³ BN116_11 Page 17.

²¹⁴ OH ACDHPT 26th November 2018.

²¹⁵ LandesArchiv 13198 (trans) Memorandum from Amon with a summary of Primodos page 64.

²¹⁶ *'Don't tell the patient: Behind the drug safety net' Highland Park 1999 (p89) 'I wrote to Mr. Baggott [the claimant's lawyer] saying that he would be welcome to make whatever use he liked of my published works but that I could not let him see the original records on which they were based and which would identify the patients and their doctors... Any disclosure of medical records supplied in confidence by doctors would have been a disaster for further work in drug safety or, indeed, in any surveys involving the use of confidential medical records. If it became known that a voluntary report addressed to the Committee on Safety of Medicines or any information obtained during a follow-up by one of our medical field workers could be produced in court either in this country or in the United States as part of the evidence in an entirely unconnected case, this would certainly be the end of the Committee's yellow card system. No doctor would ever co-operate again. There was no question that I was going to show the personal records of several thousand cases to Mr Baggott...'*

- 3.94 Pre-trial Schering had 28 expert reports on causation;²¹⁷ the legally-aided claimants had far fewer. It has been suggested that the financial disparity between the parties contributed to the claimants' difficulties in securing experts. The memo on the Bermuda symposium goes on to say about Dr Inman *'He made it clear that he wanted to quit his service with the authorities and go to the university.'*²¹⁸ In a 2014 debate on Oral Hormone Pregnancy Tests Yasmin Qureshi MP stated *'I have no hesitation in saying that those witnesses were bought off by Schering. It is amazing how all of them ended up opening research centres, which, as everybody knows, costs money.'*²¹⁹ Bayer have confirmed to us that Schering experts were paid consultation fees at the normal rates.²²⁰
- 3.95 Eventually it was the Plaintiffs who applied to discontinue their claim as their counsel had concluded that they did not have a reasonable prospect of proving causation. In July 1982 the case was discontinued, but not dismissed as the Plaintiffs were children. The judge recorded *'The effect of that order is not to shut out the Plaintiffs absolutely. It is open to them to apply in the future in the event of a scientific revolution or a marked change in the circumstances. I should, however, make it clear that for leave to be given on any future occasion a very strong case indeed would have to be made out by the Plaintiffs to show that it was just for the matter to be re-opened, and the Court would have to be satisfied that no unreasonable prejudice to the Defendants would accrue. I think it is very unlikely that leave to the Plaintiffs would be given, but I think that it is in all the circumstances just that the door should be kept open to that very limited extent.'*²²¹

Recent campaigning activity

- 3.96 In 2009 the ACDHPT was relaunched. Legal aid was obtained to investigate whether scientific findings since 1982 could lead to a reopening of the litigation. In 2012 Professor Steve Robson commissioned the UK Teratology Information Service (UKTIS) to review the post-1982 literature published on Oral Contraceptives and

²¹⁷ *'D' and others v Schering Chemicals Ltd and 'R' and another v Schering Chemicals Ltd*, Judgment of Mr Justice Bingham (QBD, 2 July 1982) (unreported), see Bayer's written evidence to the IMMDS Review Attachment 6.

²¹⁸ After leaving the Civil Service Dr Inman went on to found the Drug Safety Research Unit. <http://www.dsru.org/> The initial funding of the DRSU is discussed in his autobiography *'Don't tell the patient: Behind the drug safety net'* Highland Park 1999.

²¹⁹ HC Deb (23 October 2014) Vol 586, Col 1118 Available at <https://hansard.parliament.uk/Commons/2014-10-23/debates/14102384000001/OralHormonePregnancyTests>

²²⁰ Q22 Bayer's written evidence to the Review – Attachment 6.

²²¹ See FN 99.

HPTs.²²² Professor Robson used the UKTIS review to inform a legal report he wrote for individuals who were considering claiming against Bayer. The UKTIS review concluded *‘The single study published post-1982 on Primodos does not demonstrate an association between Primodos exposure in pregnancy and an increased overall risk or specific pattern of congenital malformation in exposed offspring.’*

- 3.97 From 2010 onwards questions on the adverse effects from HPTs were raised in both Houses of Parliament. In 2012 an Early Day Motion was tabled by Yasmin Qureshi MP calling for a public inquiry into the needs of affected people, the eight year gap between Gal’s paper and the CSM warning and the prescribing of HPTs after 1975.
- 3.98 In January 2014 Yasmin Qureshi MP and Dr Dan Poulter MP, the Parliamentary Under Secretary for Health, met the Medicines and Healthcare products Regulatory Agency (MHRA). Dr Poulter asked the MHRA to review the historic evidence. In March 2014 the MHRA published ‘Assessment of historical evidence on Primodos and congenital malformations.’²²³ This report looked at 36 published studies and concluded *‘Having carefully considered the available published evidence, our position therefore remains that the data are not sufficient to conclude that there is a causal association between the use of Primodos (or any HPT) and congenital abnormalities.’*
- 3.99 On 23 October 2014 a House of Commons debate on Oral Hormone Pregnancy Tests initiated by Yasmin Qureshi MP took place. In his speech, George Freeman MP, the Parliamentary Under Secretary for Health, agreed to the establishment of an independent expert working group on HPTs.²²⁴

The expert working group on hormone pregnancy tests

- 3.100 The CHM set up the Expert Working Group on Hormone Pregnancy Tests (EWG) to investigate the issue of an association between the use of HPTs and congenital malformations. This included holding a public call for evidence, obtaining evidence from the National Archives and the LandesArchiv in Germany, and other published research.

²²² Expert Working Group on Hormone Pregnancy Tests Meeting minutes and Declarations of Interest, available https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

²²³ MHRA ‘Assessment of historical evidence on Primodos and congenital malformations.’ March 2014 <https://webarchive.nationalarchives.gov.uk/20141204145033/http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con404471.pdf>

²²⁴ HC Deb (23 October 2014) Vol 586, Col 1118 Available at <https://hansard.parliament.uk/Commons/2014-10-23/debates/14102384000001/OralHormonePregnancyTests>

- 3.101 At this point we should note our Terms of Reference *‘It is not the intention of the Review to re-do the work recently undertaken by other Reviews/ Expert Working Groups’*. Our remit is to *‘focus on whether the processes pursued to date when safety concerns have been raised by patients, their families and others have been sufficient and satisfactory’*.
- 3.102 The MHRA told us²²⁵ that each participant was given a copy of the guidance – *‘HPT – Participation Definitions’* which included what would be considered a conflict of interest for each category of attendee – and was asked to sign a conflict of interests form. The Chair opened the EWG inquiry by reminding participants to declare any personal interest in HPT manufacturers and their successor companies and to declare the nature of any involvement they might have had with HPTs.²²⁶ The issue of potential conflicts arising from involvement in related litigation was also raised. Subsequently, concerns over perceived conflicts of two EWG members were raised by the ACDHPT Chair. The EWG acknowledged that, whilst a terminated consultancy would not necessarily have precluded one particular expert from being on the Group (as it was not current), it would not, however be appropriate for him to continue as an invited expert. In fact, he no longer participated in the EWG, as is recorded in the minutes of the third EWG meeting.²²⁷ In the other case the EWG concluded there was not a conflict of interest.
- 3.103 The MHRA acknowledged²²⁸ that *‘We accept the need to review our policies and processes in light of the concerns expressed in the context of the Review’*. The Review welcomes this and would suggest that more thorough checks are undertaken in the future to ensure that there is no conflict of interest of any potential member (whether actual or perceived). Particular care needs to be taken in contentious areas regarding past associations and interests. **Future EWGs should consider what is proportionate and whether they should proactively check potential members’ interests prior to their appointment.**
- 3.104 In her evidence to us Mrs Marie Lyon, Chair of the ACDHPT, raised the issue of observer status, stating as follows: *‘The statement again from the Expert Working Group from Dr Gebbie [Chair of the EWG] was that I was invited to comment after every Expert Working Group meeting. This is absolutely untrue. I was publicly admonished by the Chair at the first – at the very first – meeting, when I attempted*

²²⁵ See the right of reply to the ACDHPT Oral evidence given on 14 February 2019 from the Chair of the EWG (dated 1st May 2019) and also the Right of Reply from the MHRA (dated 24th April 2019).

²²⁶ Expert Working Group on Hormone Pregnancy Tests Meeting minutes and Declarations of Interest, available https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

²²⁷ See the minutes from the third EWG meeting, *ibid*.

²²⁸ MHRA right of reply dated 3rd July 2019 to the OH ACDHPT 14th February 2019.

*to question a statement from the MHRA. I was told I should not have attempted to speak as I had observer status only and would not be allowed to contribute unless invited by the chair'. The minutes of the first meeting record: 'Mrs Lyon raised concerns about the restrictions of observer participation. The Chair reassured Mrs Lyon that she would make a point to ask her to contribute.'*²²⁹

- 3.105 In the guidance, which was given to each participant, Observer status was defined as *'Able to respond to questions from members or Chair as necessary but do not contribute to the conclusions and recommendations.'* **In our view, experiences of those directly affected and other lay representatives can add great value and every effort should be made to facilitate and support their involvement, which includes both asking and answering questions at appropriate points of the meeting.**
- 3.106 The issue of a possible as opposed to a causal association has been a major controversy. A possible association means HPTs might have caused malformations, a causal association confirms that HPTs did cause malformations. The terms of reference for the EWG were agreed in the first meeting. Their first term of reference was *'To consider all available evidence on the possible association between exposure in pregnancy to HPTs and adverse outcomes in pregnancy (in particular congenital anomalies, miscarriage and stillbirth) including consideration of any potential mechanism of action'*. This does not mention a causal association.
- 3.107 In their oral evidence²³⁰ to us the EWG were clear that they could not and have not precluded a possible association between HPT use and damage to babies. The Chair said *'In our terms of reference the first sentence was to consider all available evidence and possible association. Again, we know there's a possible association. That was why we were doing the report. But then when the report came out, we were criticised because we hadn't actually picked up on saying was there a possible association or not. But there is a possible association.'*
- 3.108 The EWG function was to assess the scientific studies and, they were convened because a possible association existed.²³¹ The heart of the HPT controversy has been what scientific evidence would be needed for an acceptable level of proof of causation. We recognise why causation is so important. In our view clearer Terms of Reference and more effective communication may have led to a better

²²⁹ OH ACDHPT 14th February 2019, and the Chair of the EWG's right of reply to these criticisms dated 24th April 2019 and the MHRA right of reply dated 3rd July 2019.

²³⁰ OH EWG 28th January 2019.

²³¹ See the right of reply from the Chair of the EWG dated 1st May 2019 and also the right of reply from the MHRA dated 24th April 2019 both in response to the ACDHPT Oral evidence given on 14th February 2019.

- understanding of what the EWG were tasked to examine and may have prevented the distress caused.
- 3.109 The treatment of families from the ACDHPT who attended to give evidence to the EWG was raised in our oral evidence sessions by the ACDHPT, the HPT All-Party Parliamentary Group (APPG), the MHRA, and also by the EWG. The EWG Chair acknowledged that this had been a difficult experience for some *‘I think we might have done more to support the families. They came on a busy afternoon of work. We had a fleeting opportunity to speak to them. They were very upset. Then I think, inevitably, the conclusions of the report were very disappointing, so I think if – we could have spent more time speaking to them and helping them understand the language and the scientific methods.’*
- 3.110 Similarly, in their right of reply response to oral evidence given by ACDHPT the MHRA wrote *‘The MHRA has reflected carefully on this experience and has apologised sincerely for any unintentional distress felt by the families. We are taking this matter seriously and are now introducing changes to how we interact with patients, families and carers.’*²³²
- 3.111 We note that the MHRA provided the secretariat to the EWG. The Chair of the EWG told us the secretarial support had been excellent. In the EWG’s third meeting, concern was expressed by some EWG participants that large volumes of documents had been sent with very little time to read them. The EWG minutes note that the EWG were offered the chance to postpone the meeting but did not do so.²³³
- 3.112 The EWG decision-making meetings did not include the experts giving evidence or the ACDHPT patient representatives. In their role as the secretariat, some MHRA staff were present during EWG decision-making. During our own observations of the processes adopted by the two ad hoc expert working groups, we did not observe any examples of interference by the secretariat in the decision-making process. However, the potential exists. **To ensure future EWG decisions are beyond reproach, we recommend that the CHM consider using an independent secretariat for EWGs.**
- 3.113 Confidentiality agreements by those participating in the working group were another area of concern.²³⁴ We recognise the need for a process to be carried out

²³² Right of Reply from the MHRA dated 22nd April 2019.

²³³ Expert Working Group on Hormone Pregnancy Tests Meeting minutes and Declarations of Interest, available https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

²³⁴ This issue was raised by parliamentarians and by Prof Carl Heneghan, HC Deb (23 April 2019) Vol 658, Col 207WH Available at <https://hansard.parliament.uk/Commons/2019-04-23/debates/E521E633-CDA2-4E91-95FE-4549A62C2973/HormonePregnancyTests> and OH Professor Carl Heneghan 27th November 2018.

with an appropriate degree of confidentiality. However, this must be balanced against the rights of participants to hold an EWG to account. We recommend that the CHM review their confidentially agreements accordingly.

- 3.114 At their fifth meeting the EWG heard from Dr Neil Vargesson on his preliminary work on the impact of the components of Primodos on zebrafish and chick development. This work was later published as Brown et al 2018 (see paragraph 3.121). In a letter to the EWG Mrs Lyon criticised the time allotted to Dr Vargesson.²³⁵ The EWG examined Dr Vargesson's work, and it is not our remit to determine what importance should be attached to a piece of scientific research. His work was re-examined after publication by an ad hoc EWG and by the EMA.²³⁶
- 3.115 In the final EWG meeting on 27 March 2017 *'The Group discussed whether the data were amenable to a meta-analysis and agreed that because the studies were so different such an analysis would not be informative but that this point should be made clear in the report.'* It is not for us to assess the validity of this decision. The minutes stated *'The Members concluded that there was no clear evidence that taking Primodos during the first trimester of pregnancy could cause congenital anomalies via a direct pharmacological action; however, because the evidence was limited and many factors remained unclear, such an effect could not be definitively excluded.'*²³⁷
- 3.116 A draft report was sent to the CHM for review. When we discussed peer review with the Chair of the EWG she said *'we were reporting to the CHM and, in essence, that's exactly what they did. We completed the report and submitted it to them.'*²³⁸ We have seen the draft and final reports and the changes that were made.
- 3.117 It is standard practice for amendments to be made between draft and final versions and the EWG have every right to change their draft report in response to feedback. When asked in oral evidence²³⁹ about these changes the Chair replied *'We clarified – they [CHM] felt our wording was not clear enough, so we did reword some of the findings, but nothing was changed.'* However, in our view, the draft and final versions potentially create different impressions in the mind of the reader, and

²³⁵ Expert Working Group on Hormone Pregnancy Tests Meeting minutes and Declarations of Interest, available https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

²³⁶ Professor Vargesson's work is ongoing. Should his, or anyone else's, research produce relevant results we understand that further ad-hoc EWGs will be convened.

²³⁷ Expert Working Group on Hormone Pregnancy Tests Meeting minutes and Declarations of Interest, available https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/667482/Minutes-declaration-of-interests-redacted.pdf

²³⁸ OH EWG 28th January 2019.

²³⁹ *ibid.*

we understand why the changes to a more definitive conclusion in the final report could have been distressing to campaigners.

- 3.118 The CHM commissioned an EWG in order to provide an independent, expert viewpoint. None of the evidence that the EWG has supplied to us has suggested that the CHM in any way pressured them to change their report. **However, to avoid any perception of undue influence, it is good practice for any similar report to be reviewed by an independent panel of experts.** We suggested this to the EWG, and Professor Evans said *‘I think that we might have done something better on that, but that would have required creating a precedent for reviews of the Commission on Human Medicines that hasn’t existed in the past. I think that there are reasons to say one might suggest doing that in the future, but it’s a very different way of working.’*²⁴⁰
- 3.119 Once the EWG report was published it was met with considerable disquiet from the Chair of the ACDHPT and Yasmin Qureshi MP, who termed it a whitewash.²⁴¹ Further dissatisfaction was expressed by parliamentarians in a Westminster Hall debate on hormone pregnancy tests on 23 April 2019.²⁴² Our observations on process, if acted upon, should help mitigate against this in future.

Sky Documentary

- 3.120 On 21 March 2017 a Sky News documentary *Primodos: The Secret Drug Scandal*, presented by Jason Farrell, was broadcast.²⁴³ This documentary used material from the LandesArchiv Berlin and the National Archives as well as interviewing affected individuals. This documentary covered a range of aspects of HPT use, including some that were outside the EWG’s remit. The alleged behaviour and knowledge of the manufacturer Schering was examined, including the lack of pre-market testing, keeping the product on the market after safety concerns had been raised, the manufacturer’s awareness that the product was believed to act as an abortifacient in some countries, and their relationship with the UK drug regulator. The programme also examined the response of the UK drug regulator over HPTs, particularly Dr Inman.

²⁴⁰ *ibid.*

²⁴¹ Holly Watt *Anger after report finds birth defects not caused by hormone pregnancy tests* The Guardian 15 November 2017 available at <https://www.theguardian.com/society/2017/nov/15/1960s-hormone-pregnancy-test-did-not-cause-birth-defects-review-finds>

²⁴² HC Deb (23 April 2019) Vol 658, Col 207WH Available at <https://hansard.parliament.uk/Commons/2019-04-23/debates/E521E633-CDA2-4E91-95FE-4549A62C2973/HormonePregnancyTests>

²⁴³ *Primodos: The Secret Drug Scandal*. Jason Farrell, Sky News, March 2017

The Zebrafish ad hoc Expert Working Group.

- 3.121 As noted above, Professor Vargesson's research was published as Brown et al in Nature Scientific Notes in February 2018. Zebrafish embryos had limb deformities, vascular disruption, yolk sac and eye anomalies after exposure to Primodos components.
- 3.122 The CHM convened a new ad hoc EWG consisting of different scientists from the original EWG. It examined the suitability of the zebrafish model for evaluating EE and norethisterone effects in human pregnancy, looking particularly at the study's robustness and any clinical implications. The MHRA also made a referral²⁴⁴ to the EMA's CHMP asking for a scientific opinion on these points.
- 3.123 The zebrafish ad hoc working group met in October 2018 to consider Brown et al, including a presentation from Professor Vargesson.²⁴⁵ They concluded *'Developmental effects occurred at concentrations in the zebrafish embryo that were several orders of magnitude higher than would occur following clinical doses. Consequently, the Group considered that the Brown et al., 2018 study should be considered with the existing evidence as part of the overall weight of evidence and concluded that the study does not raise any new safety concerns for products in clinical use containing norethisterone acetate and ethinylestradiol.'*
- 3.124 The CHMP report came out in the same month.²⁴⁶ Professor Vargesson expressed concern that he had not been asked to present his findings to the CHMP nor to attend the meeting. He had had a short phone call with the rapporteur. Having observed the CHMP meeting it was clear that CHMP had processes in place for asking for information from Professor Vargesson and it was open to them to seek further information had they felt it would have aided their decision-making. Their findings were: *'Overall, due to the multiple limitations of the study described in the manuscript (Brown et al., 2018) the results of this study do not add to the current knowledge regarding adverse events in early pregnancy in humans. The CHMP concluded that there are no new clinical implications based on the results of the presented zebrafish study.'*

²⁴⁴ Under article 5(3) of Regulation EC 726/2004.

²⁴⁵ Report of the Commission on Human Medicines ad hoc Expert Group on Evaluation of new Research on the Developmental Effects of norethisterone acetate and ethinylestradiol in zebrafish embryos available at <https://www.gov.uk/government/publications/chm-ad-hoc-expert-group-evaluation-of-new-research-on-the-developmental-effects-of-norethisterone-acetate-and-ethinylestradiol-in-zebrafish-embryos>

²⁴⁶ Assessment report for Article 5(3) procedure: Norethisterone and ethinylestradiol (EMA/H/A-5(3)/1470) available at https://www.ema.europa.eu/en/documents/report/assessment-report-article-53-procedure-norethisterone-ethinylestradiol_en.pdf

Heneghan et al meta-analysis

- 3.125 The question of whether the EWG had, in fact, undertaken a meta-analysis was raised. There is a comment at the base of one of the Forest plots in the EWG report and Annex 27 which reads *‘NOTE: Weights are from random effects analysis.’* Prof Heneghan told us in his oral testimony *‘...Somebody somewhere in the EWG did perform a meta analysis; they just didn’t report it.’*²⁴⁷ There was no meta-analysis included in the EWG report. We asked the EWG for clarification of this point. They said that the comment was an artefact of the software that had been used to draw the Forest plots. They confirmed that they had not undertaken a meta-analysis.²⁴⁸
- 3.126 In October 2018 the first version of the Heneghan et al meta-analysis was published.²⁴⁹ It stated *‘This systematic review and meta-analysis shows that use of oral HPTs in pregnancy is associated with increased risks of congenital malformations.’*
- 3.127 In response the CHM convened a new ad hoc EWG to examine the suitability and robustness of the methodology, including the selection and application of the data quality score, and any clinical implications. The MHRA also made a referral to CHMP at the European Medicines Agency with the same remit as the ad hoc EWG.
- 3.128 On 30 January 2019 a Freedom of Information (FOI) request was made by Yasmin Qureshi MP to the MHRA for the raw data used by the EWG. Mrs Lyon made a similar request on 4 February. On 20 February Mrs Lyon sought our assistance in obtaining this data, so we emailed the MHRA. The raw data was sent to Mrs Lyon on 8 March. The MHRA stated that *‘All raw data that were used in the forest plots in the EWG report are available in the published papers.’*²⁵⁰
- 3.129 On 18 March 2019 the EWG ad hoc group met to consider the Heneghan meta-analysis. Prof Heneghan and Dr Aronson attended and presented their research.
- 3.130 In a Westminster Hall debate on HPTs on 23 April 2019 the FOI request for the raw data was raised, questioning if the EWG had done a meta-analysis but not included it, and highlighting that the MHRA is part-funded by the pharmaceutical industry.

²⁴⁷ OH Professor Carl Heneghan 27th November 2018.

²⁴⁸ OH EWG 28th January 2019.

²⁴⁹ Heneghan, C et al. “Oral hormone pregnancy tests and the risks of congenital malformations: a systematic review and meta-analysis” *F1000Research* 2019: 7, 1725 <https://doi.org/10.12688/f1000research.16758.2>

²⁵⁰ OH ACDHPT Oral 14th February 2019; see also the right of reply from the MHRA dated 24 April 2019.

- 3.131 Both the CHMP report and the ad hoc expert working group reports were published on 6 May 2019.²⁵¹ The CHMP concluded *‘Therefore, the quality of most studies used is questioned and, as a result, the conclusions of the meta-analysis cannot be considered reliable. Due to the multiple limitations of the meta-analysis study, the results described in this manuscript cannot be used to further expand clinical knowledge.’* The ad hoc expert working group report states *‘...Members advised that the methods used were not in line with best practice, the application and choice of NOS²⁵² [Newcastle-Ottawa Scale] was questionable, and the study could not be considered robust. The Members further advised that due to limitations in the design, reporting and analysis of the included studies there would be little value in re-analysing the data.’*
- 3.132 The ACDHPT rejected these reports. They queried the experts chosen for the ad hoc review of the Heneghan paper, which the CHM later defended.²⁵³ They were concerned that the Chair of the CHMP had been employed by Bayer, this was before Bayer bought Schering in 2006. In our view this should have been declared for transparency. Both CHMP opinions were agreed without a vote.

Litigation

- 3.133 In August 2019 solicitors sent out letters before action to Bayer and Sanofi²⁵⁴ and to the Secretary of State for Health and Social Care. We understand they are now preparing to file a class action. Should this proceed, then the Court may determine the issues of causation and possibly compensation.

Conclusion

- 3.134 It is our view that from 1967, hormone pregnancy tests should no longer have been available. An alternative to HPTs was available, and the expression of any concern about risk should have led to action by the regulator. Failure to act meant

²⁵¹ CHM ad hoc Expert Group: Evaluation of systematic review and meta-analysis of studies on oral Hormone Pregnancy Tests by Heneghan et al (6 May 2019) available at <https://www.gov.uk/government/publications/chm-ad-hoc-expert-group-evaluation-of-systematic-review-and-meta-analysis-of-studies-on-oral-hormone-pregnancy-tests-by-heneghan-et-al>; Assessment report:

Procedure under Article 5(3) of Regulation (EC) No 726/2004 Norethisterone and ethinylestradiol (26 April 2019) available at https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-norethisterone-ethinylestradiol-emea/h/53/1477_en.pdf

²⁵² The *Newcastle-Ottawa Scale* (NOS) is a risk of bias assessment tool for observational studies that is recommended by the Cochrane Collaboration when carrying out a meta-analysis of such studies.

²⁵³ OH ACDHPT Oral 14th February 2019; see also the right of reply from the Chair of the EWG dated 1 May 2019 and the right of reply from the MHRA dated 24 April 2019.

²⁵⁴ They are the companies that acquired Schering and Roussel respectively.

that women were exposed unnecessarily to a potential risk. We are not judging the actions of the past by the standards of today – contemporaneous thinking agreed with the approach that *‘it would be morally indefensible to put the suspicion to the test’* (see paragraph 3.45).

- 3.135 It has been over forty years since HPTs were removed from the UK market and the struggles campaigners have had to be heard have been substantial. A possible association between HPTs and malformations exists and cannot be precluded, as was stated by EWG members during oral evidence, and this Review cannot resolve matters of causation. However, we recognise the struggle, anxiety and guilt of those affected and believe they are entitled to support. Our more general recommendations can be found in Chapters 1 and 2. Here we set out areas for improvement that are specific to hormone pregnancy tests.

Meeting the needs of those affected

- 3.136 **Specialist centres should be established for all families adversely affected by medicines taken in pregnancy, to provide integrated medical and social care expertise to enable those affected to access the services they need in one place (Chapter 1, Recommendation 5).** These centres should provide a single place for diagnosis, including genetic testing, and to co-ordinate referrals to other services. When establishing these centres, it should be considered how they can work with existing local services. These centres should also be responsible for carrying out and publishing research, including on long-term outcomes. It should be for the experts at these centres to decide on the specific services offered.
- 3.137 **An *ex gratia* scheme to provide discretionary payments should be established (Chapter 1, Recommendation 4).** Our Terms of Reference state that we will not consider individual compensation, but we will consider wider systems of redress. In the case of hormone pregnancy tests, casual association has not been established, however in view of the stress, anxiety, psychological harm, and toll of fighting for recognition, we feel that it would be appropriate for a discretionary scheme to be set up to provide redress.

The working of expert groups

- 3.138 In paragraphs 3.103, 3.105, 3.112 and 3.118 we have highlighted improvements for future EWG process. However, we do not believe the procedural issues we have noted would have altered the EWG conclusions.

Preventing future harms

- 3.139 In 1967 pregnancy testing with HPTs should have been stopped. In our view neither the CSD nor the manufacturers responded in a sufficiently precautionary way to concerns around HPTs in 1967. Further opportunities for CSD/CSM to act were missed at each of their interim study results (paragraph 3.74).
- 3.140 The effectiveness of regulatory actions over HPTs was inadequate. Although the UK was one of the first countries to act on HPTs by removing the indication in 1970, this was done without any accompanying warning of the concerns raised at that time. Nor was it effectively communicated either to doctors or within the DHSS. Even after the 1975 warning, which was sent to doctors, HPTs were still used for pregnancy testing. This lack of regulatory effectiveness is neither limited to HPTs nor, sadly, is it a historic issue. While there have been substantial changes to the regulatory system since hormone pregnancy tests were on the market, we believe that further improvements should be made to prevent future harm. We set these out in our recommendations in **Chapter 1, Recommendation 6** and in **Chapter 2, Theme 11**.

- In 1967 HPTs should have been withdrawn as pregnancy tests given concerns about risk and the availability of non-invasive alternatives. This was years earlier than they were withdrawn.
- When the indication was removed in 1970 the system failed to prevent HPTs being provided/prescribed, thus exposing more women and their babies to HPTs during pregnancy.
- An apology is due, and support is required for those who have suffered avoidable harm.
- Those affected are not receiving adequate support. We recommend that specialist centres are established for all families adversely affected by medications taken during pregnancy, to provide integrated medical and social care expertise to enable those affected to access the services they need in one place.
- The question of causality was outside our scope, but we note that it has been addressed by others and it may be revisited in the prospective legal action.
- We also make recommendations to reduce the risk of exposure to suspected or known teratogens.

Actions for Improvement	
MHRA/CHM need to review their EWG processes, specifically: – whether they should consider proactively checking potential members' interests prior to their appointment; – how to best support the involvement of affected and other lay individuals in EWG meetings, including both asking and answering questions at appropriate points of the meeting; – whether an independent secretariat should be used for EWGs; – whether EWG reports should be reviewed by an independent panel of experts.	3.103, 3.105, 3.112, 3.118
See Chapter 1, Recommendation 5	3.136
See Chapter 1, Recommendation 4	3.137

4 Sodium valproate use in pregnancy

'People need to be held accountable for how this drug has been allowed to be prescribed to pregnant women and the lifelong effects this is having on the individuals affected... we need to stop this happening to anyone else in the future.'

'I felt so guilty, I felt it was my fault for his problems and disability... not to be told what these tablets can do and have done to many families is terrible.'

'If I'd been told my baby could be damaged by the medication, I was taking I would not have taken it. All our hopes and dreams were destroyed by this, but we love our son dearly. We weep for the child who could have been and the man who never was.'

Parents of those affected by sodium valproate exposure during pregnancy

Introduction and summary

- 4.1 Sodium valproate and related medicines,²⁵⁵ commonly known by brand names including Epilim, Episenta and Depakote, are licensed in the UK to treat epilepsy and bipolar disorder. These medications are also used for migraine prophylaxis, and pain management. Approximately 27,000 women of childbearing age take valproate in the UK.²⁵⁶ Sodium valproate is an essential medicine for many men and women with epilepsy for whom other treatments might not be effective. Since 1972, when sodium valproate was first licensed in the UK to treat epilepsy, evidence has emerged that it can cause physical and neurodevelopmental effects in children if taken by mothers during pregnancy. This group of features is currently termed as 'Foetal Valproate Spectrum Disorder' (FVSD). FVSD will be added to the next WHO International Classification of Diseases, ICD-11 following campaigning by patients.

²⁵⁵ Valproic acid is used in the UK as the sodium salt (sodium valproate) and a mixture of valproic acid and sodium valproate, known in particular proportions as divalproex sodium or valproate semisodium. The magnesium salt (magnesium valproate) is also used in other parts of the world. In this report we will refer to sodium valproate to refer to the group of valproic acid-based medications used in the UK.

²⁵⁶ Specialist Pharmacy Services <https://www.sps.nhs.uk/repositories/prescribing-of-valproate-in-the-line-with-valproate-pregnancy-prevention-program-prevent-policy/>

- 4.2 In 1972, at the time of licensing of sodium valproate, it was known to be teratogenic (harmful to a developing foetus) in animals. Information provided to prescribing doctors via the datasheet stated that sodium valproate should only be used in severe and resistant cases of epilepsy and was known to be teratogenic in animals. Data on the risks of valproate use during pregnancy emerged in the academic literature from the early 1980s. This suggested an association between sodium valproate exposure in utero, and physical malformations, with the ‘Foetal Valproate Syndrome’ being described in 1984.²⁵⁷
- 4.3 While there were concerns about the teratogenicity of other antiepileptic drugs during this period, doctors were advised that the risk did not justify *‘discouraging a woman who needs anticonvulsant treatment from having a child or changing a satisfactory drug regimen when the epilepsy is well controlled.’*²⁵⁸ Information in the datasheet for sodium valproate was updated to include advice on monitoring and breastfeeding in 1984, about risks of neural tube defects in 1990, and associations with further congenital malformations were added over time. During the early 2000s, evidence emerged of a neurodevelopmental effect of sodium valproate exposure during pregnancy. Warnings to doctors (via the datasheet or summary of product characteristics (SmPC)) about an association with development delay were included in 2003, verbal IQ in 2005, and reports of autism spectrum disorders in 2010.
- 4.4 Advice to doctors developed over time, and in 2004, National Institute for Health and Care Excellence (NICE) guidance clearly stated it was the responsibility of the clinician to give accurate information and counselling, tailored to individual need, to enable girls and women to make informed decisions.²⁵⁹ Up until 1994, when legislation came into force setting out what information should be included in patient information leaflets, patients would have needed to consult their doctor for information about the risks of taking valproate during pregnancy. We have heard from many women that their doctors dismissed their concerns before their pregnancies, preventing them from making an informed choice, or afterwards, when their child was affected by FVSD, impacting their ability to access support or make decisions about subsequent pregnancies.
- 4.5 In the 1990s, a number of women and children alleging that exposure to sodium valproate in utero had caused damage, and that they had not been warned of the risks, brought claims against the NHS Litigation Authority (now NHS Resolution),

²⁵⁷ For example, see the written evidence provided to the Review by Professor Jill Clayton-Smith and colleagues

²⁵⁸ ‘Teratogenic risks of antiepileptic drugs’ British Medical Journal (Clinical research ed.) 1981: **283**, 515.

²⁵⁹ NICE. CG20 The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care (2004).

and subsequently against Sanofi²⁶⁰, the principal manufacturer of sodium valproate, in 2003. Legal aid for this case was withdrawn in 2006, and restored, only for it to be withdrawn again in November 2010, a few weeks before the trial was due to start. In 2015, the All-Party Parliamentary Group (APPG) for Anti-Epileptic Drugs in Pregnancy was set up, becoming independent of the APPG for Harmful Drugs. In September 2016 it was renamed the APPG for Valproate and Other Anti-Epileptic Drugs in Pregnancy.

- 4.6 More than forty years after valproate was introduced to the market, two recent Europe-wide reviews have considered the use of valproate in women of childbearing potential. In the UK this resulted in the launch of a valproate ‘Toolkit’ in 2016,²⁶¹ which provided information for patients and healthcare professionals, and the Pregnancy Prevention Programme (PPP) in 2018.²⁶² Currently all girls and women of childbearing potential should only be treated with valproate if the conditions of the PPP are met:
- They should have received counselling about the risks of valproate treatment and the need for effective contraception and have signed a Risk Acknowledgement Form
 - They are on highly effective contraception
 - They are reviewed by their specialist at least annually
- 4.7 Valproate may still be prescribed in pregnancy to women with epilepsy who are resistant or intolerant to other treatments. This use is unlicensed, even when treatment is based on an informed choice made by the patient. In these situations, the woman and her specialist must still sign the Acknowledgement of Risk Form to confirm that options for switching treatment have been discussed, and the woman is fully aware of the risks of pregnancy whilst on valproate, and has had the opportunity for counselling about the risks.²⁶³
- 4.8 This Review has heard from families who did not receive information about the risks of treatment with sodium valproate during pregnancy. This prevented women from making informed choices about their treatment and family planning options,

²⁶⁰ The original product licence was held by Pharmacy Products (UK) Limited, a joint venture between Labaz Group and Reckitt & Colman. Sanofi acquired the Labaz group in 1981.

²⁶¹ <https://webarchive.nationalarchives.gov.uk/20170517234711/https://www.gov.uk/government/publications/toolkit-on-the-risks-of-valproate-medicines-in-female-patients>

²⁶² https://www.ema.europa.eu/en/documents/press-release/prac-recommends-new-measures-avoid-valproate-exposure-pregnancy_en.pdf

²⁶³ As set out in the Annual Risk Acknowledgement Form ‘VALPROATE HAS RISKS IN PREGNANCY’ (April 2019 version): https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/794114/Valp-ARAF-March-2019.pdf

and has led to life-long impacts on their families. Despite the efforts of the PPP, women are still becoming pregnant whilst on valproate without any knowledge of the risks. This means that babies are still being born today – estimates suggest hundreds a year – exposed to sodium valproate despite the teratogenic risk being well recognised and undisputed. This has been immensely distressing for patient groups, and frustrating for those responsible for implementing the programme. In response we have pressed the NHS at the highest level to pick up this initiative from the centre to ensure that all women on sodium valproate are provided with the information they need to make a choice about their family planning options.

4.9 We believe that it has taken far too long for serious action to be taken to reduce the number of women who take sodium valproate during pregnancy while unaware of the risk. Women were not given the information they needed to make an informed choice, and despite the efforts of the valproate toolkit and the PPP, too many women still do not have this information. Access to a diagnosis of FVSD, and to the care and support individuals and families need, is not what it should be. In addition, we cannot be sure that today the system is adequately regulating and monitoring new antiepileptic drugs. In paragraphs 4.90 – 4.106 we set out the actions we believe need to be taken to minimise harm and better support those already affected, including:

- Continuing to improve communication of risks to ensure that all women on sodium valproate are aware of the risks prior to family planning decisions.
- Identifying all of those affected by exposure to sodium valproate in utero to ensure access to support.
- Establishing specialist centres for families affected by teratogenic medication.
- An *ex gratia* scheme to provide need-based payments to help those affected by valproate exposure. In our view both the government and Sanofi should contribute to this scheme.
- Long-term data collection of women on all antiepileptic drugs (AEDs) and their children.
- Measures to reduce and monitor effects of other medications which are regularly taken during pregnancy, and are considered to have teratogenic potential, or known risk above that of the general population.

What we have heard from the patient groups and affected individuals

- 4.10 Patient campaign groups have been at the forefront of raising concerns about the use of anticonvulsant drugs during pregnancy for many years. Many felt that no-one listened to their concerns; particularly not the healthcare professionals or organisations who could have taken action. Through campaigns, social media groups, and protests, the media, engaging with their local Members of Parliament (MPs), and conducting their own research, these groups have campaigned tirelessly to bring about change. They should not have had to do this for a medication that was a known teratogen.
- 4.11 The first major action, the ‘Valproate Toolkit’ (see paragraphs 4.65 – 4.67) was put into place in 2016, over 40 years after sodium valproate was licensed for use. Patient groups continue to campaign to ensure that healthcare professionals and those taking valproate are aware of the risks, and to improve access to diagnosis, services and support for those affected.

Impact of Foetal Valproate Spectrum Disorder on the families affected

‘My daughter will never be independent and will always be reliant on support throughout her life in every aspect... she is not even able to complete forms to claim her benefits that give her the basic requirements of life, food, roof over her head, a bed to sleep in at night and clothes to wear... I have to battle for it on her behalf because she can’t.’

Parent of child affected by in utero exposure to sodium valproate

- 4.12 Women have described their feelings of guilt that the medication they needed to control their epilepsy has harmed their children during pregnancy, and which some believe also caused miscarriages and stillbirths.²⁶⁴ In addition to the challenges some of them face from epilepsy, many have described their struggles in accessing appropriate care and support for their children. They have shared their concerns about the life-long impact on their children, some of whom discover further

²⁶⁴ The UK Teratology Information Service advises on its BUMPS (Best Use of Medicines in Pregnancy) site that one small study has shown women who took daily sodium valproate doses of 750mg or more were about three times more likely to have a miscarriage than women not receiving epilepsy treatments during pregnancy, however more research is required to confirm these findings. <https://medicinesinpregnancy.org/Medicine--pregnancy/Valproic-acid/>

problems as they get older, and their fears for the future for those who are vulnerable and unable to live independently.

- 4.13 Many young people affected by exposure to valproate in utero have described experiencing anxiety and depression as well as: loneliness, isolation from their peers and difficulties forming relationships; needing help to cope with what other people would consider ‘ordinary stuff’; concerns about their existing health issues worsening, or new health problems developing. Many expressed worries about potential risk to their own children of similar health problems. This question of whether these effects can travel through generations was considered as part of the referral to the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). The PRAC considered evidence from spontaneous reporting, epidemiological and non-clinical data, related to paternal use of valproate, and to congenital malformations in third generation offspring. They concluded that the existing evidence was insufficient to support a causal association but recommended that further research should be undertaken.²⁶⁵
- 4.14 In addition to these concerns, those who are able to do so find themselves having to provide care and support to their mothers and for their more severely affected siblings. Branwen Mann, a young person affected by exposure to sodium valproate told us: *‘The responsibilities we have... are essential, ensuring that medication is taken, that enough sleep is had, helping to manage appointments as they grow older, caring for them if they have had a seizure. I recently tried to get myself acknowledged as a carer, I was told that I could not be disabled and a carer. That does not fit with the experience of a Fetal Valproate Syndrome individual.’*²⁶⁶
- 4.15 The impact of a family having one parent with epilepsy, and one or more children with physical and/or neurodevelopmental problems from valproate exposure has been described as a ‘double disability’.²⁶⁷

²⁶⁵ Assessment report: Medicinal products containing substances related to valproate (EMA/198940/2018, 2018).

²⁶⁶ OH Young People Affected by Valproate 20th November 2018.

²⁶⁷ Leigh Day written evidence to the Review on behalf of OACS Charity and FACSaware.

What is Foetal Valproate Spectrum Disorder?

Foetal Valproate Spectrum Disorder (FVSD), previously known as Foetal Valproate Syndrome, is the name given to a pattern of birth defects, and developmental problems that may be seen in children whose mothers took the antiepileptic drug sodium valproate during pregnancy. Affected children have a higher chance of having birth defects such as cleft palate, spina bifida, heart problems, and limb defects. They may have minor physical differences such as differences in their facial features which give rise to a recognisable pattern, or bendy joints. Children with FVSD have an increased risk of language difficulties, intellectual disability, memory problems, learning and behaviour problems. In some cases, the developmental difficulties they experience may also meet the criteria for other diagnoses such as Autism Spectrum Disorder or Attention Deficit Hyperactivity Disorder.

How many people are affected by FVSD?

There has been no systematic data collection on the numbers of people affected by sodium valproate exposure in utero. Current data suggests that 10% of those exposed are affected by major congenital abnormalities, and 40% by neurodevelopmental effects, but the number of children affected is dependent on the dose of the exposure; the higher the dose the more frequently children show the physical and developmental difficulties. A reasonable estimate is approximately 20,000 people being affected in the UK by in utero exposure to valproate to date (See Annex F which provides the background to this estimate).

Access to diagnosis and service provision

'We constantly have people saying 'my son has this'... 'Is this a feature of fetal valproate syndrome?' We don't quite know. There's so much guesswork in terms of the actual medical support.'

Susan Cole, Valproate Victims

- 4.16 We have heard that families affected by FVSD have struggled to access the support and services that they need. Services offered to all disabled children and young people, including child development teams or units, have been cut in the past decade. There is evidence that these cuts have reduced access to a range of services, and has had a detrimental effect on children, young people and their

- families, including impacting educational outcomes.²⁶⁸ Reduced availability of services may be compounded because families may now have to travel further to access this care, often without independent transport (due to driving restrictions on women with epilepsy).
- 4.17 A lack of awareness of FVSD among health, social care and educational providers presents another barrier for affected families. This may delay them accessing an initial diagnosis,²⁶⁹ increase the time it takes to get appropriate referrals, and lead to a failure to understand and plan for the needs of those affected, for example, by putting in place an Education, Health and Care Plan for children and young people.
- 4.18 This has prompted some campaign groups to work with experts in the field to produce letters and summary sheets for affected individuals and their carers, general practitioners, educators and others that may require the information.²⁷⁰ We have heard, from those affected by sodium valproate exposure during pregnancy, as well as in the other intervention areas within our scope, about the additional stresses caused by the difficulty of accessing other types of support, such as Personal Independence Payment (PIP), and financial and respite support for carers (who may be the parents and those affected by valproate exposure).
- 4.19 There has been no systematic data collection on the numbers of people affected by sodium valproate exposure in utero. The Review has been provided with estimates which use birth data from the Office of National Statistics, and prescribing trends (See Annex F: Sodium valproate supporting information). In general, these estimates are based on 10% of those exposed being affected by major congenital abnormalities, and 40% by neurodevelopmental effects. The numbers provided are not directly comparable as they cover differing time periods, but a reasonable estimate is approximately 20,000 affected by in utero exposure to valproate to date. In order to adequately plan service provision, a more accurate estimate will be needed. We have taken steps to explore whether this can be achieved based on prescription reimbursement data linked to NHS number (paragraph 4.90).

²⁶⁸ British Association for Community Child Health written evidence to the Review.

²⁶⁹ For example, Professor Turnpenny raised concerns that the expertise amongst geneticists regarding FVSD may have reduced (OH Dr Bromley, Professor Clayton-Smith and Professor Turnpenny 26th November 2018).

²⁷⁰ FACS Aware written evidence to the Review; J. Clayton-Smith et al. 'Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability' *Orphanet Journal of Rare Diseases* 2019: **14**, 180.

Women were not informed of the risk

- 4.20 At the time that sodium valproate was licensed in 1972, it was known to be teratogenic in animals. Concerns had already been raised about the potential risks of other anticonvulsant drugs that were already available (See Annex C Sodium valproate timeline). Information provided to prescribing doctors stated that sodium valproate should only be used in severe and resistant cases, and was known to be teratogenic in animals. We have heard from many women that their doctors did not discuss these risks with them prior to their pregnancies, and in some instances, reassured them that their medicines were safe, or that problems their unborn baby may have could be ‘fixed’. This meant that women were deprived of the ability to make informed decisions about their treatment and family planning options.
- 4.21 Patient groups have suggested that in balancing the risks and benefits, doctors prioritised the medical treatment of epilepsy or bipolar disorder, and gave advice based on their own assumptions, without involving patients in the decision-making process. In addition, not all women have regular, if any access to a neurologist with which they can discuss concerns related to their treatment and pregnancy. Janet Williams of the Independent Fetal Anti-Convulsant Trust (INFACT) told us: *‘There’s a lot of ladies out there that haven’t got a neurologist.’*

Failure to act on emerging risk

- 4.22 Despite concerns about the teratogenicity at the time of licensing, no system was put in place to collect data on the outcomes of pregnancy in women taking sodium valproate (and other anticonvulsants). The patient groups argue that if that had taken place, the risks (including the neurodevelopmental effects) would have emerged much sooner, and we agree.
- 4.23 The patient groups also argue that the entire healthcare system has been slow to respond to these emerging risks, such as by strengthening warnings, ensuring that doctors were following guidance regarding the use of antiepileptic drugs in pregnancy, and monitoring that women were actually receiving appropriate counselling when taking valproate and/or planning pregnancy. Had they done so, many women would have been able to make different decisions about their treatment and family planning options, such as planning a change in their treatment with their neurologist before getting pregnant.

Use of valproate medicines in psychiatry

- 4.24 Our Review has focussed on valproate use in epilepsy as this was its initial licence, and remains its primary use in the UK. Valproate medicines were licensed in 2001 for the treatment of manic episodes associated with bipolar disorder, and have other uses in psychiatric practice, migraine prophylaxis and neuropathic pain management. Psychiatric uses include: treatment of manic episodes; augmentation of antidepressant drug treatment; and prophylaxis to reduce episodes of bipolar or unipolar disorder. An audit from 2018 suggests that many women of childbearing age treated for bipolar disorder with valproate are also not receiving information on the risks to the unborn child.²⁷¹
- 4.25 Professor David Baldwin of the Royal College of Psychiatrists (RCPsych) told us that psychiatric medicine differs from the treatment of epilepsy, in that *‘there are always alternatives to valproate that have similar effectiveness and roughly similar tolerability’*.²⁷² The availability of alternative methods of treatment means that the balance of benefit and risk is different in this population. Recent RCPsych guidance on prescribing valproate in women and girls of childbearing potential has stressed that valproate should never be prescribed in this group.²⁷³

Emerging concerns about valproate teratogenicity

Concerns about valproate at the time of licensing

- 4.26 Sodium valproate was first licensed for use in the treatment of epilepsy in the UK in 1972 for one year. Patient groups have raised concerns about the process of licensing the drug. A full clinical trial was not carried out in the UK,²⁷⁴ and available data from France was considered instead.²⁷⁵ At our Oral Hearings in November 2018, OACS quoted a contemporary account from an employee at Labaz, the company that was then the licence-holder in the UK, which stated *‘this was only the second time in British history that a drug was allowed in England without extensive trials’* and that *‘in less than 25 months...this product was authorised for initial sales*

²⁷¹ Paton, C *et al.* ‘A UK clinical audit addressing the quality of prescribing of sodium valproate for bipolar disorder in women of childbearing age’ *BMJ Open* 2018; 8, e020450 <https://doi.org/10.1136/bmjopen-2017-020450>

²⁷² OH Royal College of Psychiatrists 28th January 2019.

²⁷³ RCPsych ‘Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness’ 2018.

²⁷⁴ MHRA written evidence to the Review – Medicines Commission MC 76/112A ‘A Note on Epilim – Sodium Valproate’ 1976.

²⁷⁵ Reported in: US Department of Health, Education and Welfare. Workshop on Antiepileptic Drug Development, April 15 1977, Arlington, Virginia.

*in a country which was reputed to have the most stringent regulations in the world except for the United States.*²⁷⁶

- 4.27 This initial licence included conditions that sodium valproate could only be used in hospitals and other specialist centres for epilepsy (at the time, epilepsy ‘colonies’), provided all patients were monitored for therapeutic efficacy and safety, and the results reported to the licensing authority.²⁷⁷ This data, and data from animal studies, was submitted along with an application for a full product licence the following year, which was granted by the Department for Health and Social Security (DHSS) in 1974.²⁷⁸
- 4.28 The Medicines and Healthcare products Regulatory Agency (MHRA) were able to provide the assessment reports considered at the meetings of the Sub-committee on Toxicity, Clinical Trials and Therapeutic Efficiency from January 1972 and May 1972, in which the Sub-Committee recommended that decisions on licensing were deferred pending further evidence. The minutes of the meeting of the Sub-Committee in June 1972 state: *‘On the evidence before them the Sub-Committee recommend the grant of a product licence for one year for this preparation for the purposes indicated in the application provided that promotion is limited to hospitals and other centres specialising in the treatment of epilepsy, and subject to all patients being monitored for therapeutic efficacy and safety.’* The MHRA informed us²⁷⁹ they were unable to locate the paper discussed at that meeting, and that it was unclear whether this decision was based on the papers considered at the January and May meetings, or a separate further paper. The MHRA were also unable to locate the assessment report considered at the Committee on Safety of Medicines (CSM) meeting in March 1974 in which the limit on the licence was deleted. Extracts from the minutes of the meeting of the Sub-Committee on Toxicity and Clinical Trials, which advised the CSM on this issue, say that their recommendation was based on *‘...the results presented, and in particular the further data on teratology...’*²⁸⁰
- 4.29 During this period the CSM was aware of, and had their own, concerns about the risks of all anticonvulsants in pregnancy, how this should be communicated to doctors (paragraph 4.52), and inclusion of this information on the datasheets

²⁷⁶ *ibid.*

²⁷⁷ MHRA written evidence to the Review – CSM Minutes January 1972, May 1972 and June 1972. CPS minutes January 1972.

²⁷⁸ Sanofi written evidence to the Review; MHRA written evidence to the Review – CSM Minutes March 1974, September 1974.

²⁷⁹ MHRA written evidence to the Review.

²⁸⁰ MHRA written evidence to the Review.

for the relevant drugs (primidone, phenytoin and phenobarbitone).²⁸¹ The teratogenicity of valproate was considered in this context when lifting the restrictions for its use²⁸². In 1974, following the application for a full product licence, officials had sought the views of the Minister of State for Health regarding the availability of drugs which could harm the foetus. The change to the licence was agreed by the Minister *‘on the understanding [that] on the basis of animal studies, the teratogenic effects of Epilim were of the same order as phenytoin’*.²⁸³

- 4.30 A warning was agreed by the manufacturers of sodium valproate, which limited the use in women of childbearing age to *‘severe cases or those resistant to other treatment’*, provided information of teratogenicity in animals, and advised clinicians to weigh the benefits of its use against the suggested hazards. The conditions of the licence stated that these specific warnings should be included in data sheets and materials promoting the product to doctors,²⁸⁴ although a contemporary paper notes that this did not always happen.²⁸⁵
- 4.31 A position paper from the Medicines Commission in 1976 notes that valproate had been a useful drug, but that *‘had there been a category of drugs whose prescribing was restricted to specialists in the treatment of the particular disease, it is clear that Epilim would have been included in this category, at least initially until its place in the treatment of epilepsy had been assessed’*.²⁸⁶ Despite this, and earlier concerns, no follow-up was commissioned or conducted into the risk of sodium valproate use in pregnancy by the regulator at the time.
- 4.32 The Medical Research Council (MRC) supported a number of studies on epilepsy and anticonvulsant drugs during this period, but these did not include teratogenic effects.²⁸⁷ An MRC Working Party on Anticonvulsant Drugs in November 1977 considered a paper which suggested further animal studies into the method of action of teratogenicity of antiepileptic drugs.²⁸⁸ The Working Party report noted that there *‘was a great need for careful long-term toxicity studies of drugs in current use’*, and recommended that applications for trials considering the long-term effects should be sympathetically considered, and that a Co-ordinating Group should be set up with the aim of improving exchange of knowledge between clinical and basic

²⁸¹ MHRA written evidence to the Review – MC 76/112A ‘A Note on Epilim – Sodium Valproate’ 1976; National archives BN 116/17 CSM Sub-Committee on Adverse Reactions Meetings 17.1.1973-21.11.1973.

²⁸² MHRA written evidence to the Review – MC 76/112A ‘A Note on Epilim – Sodium Valproate’ 1976.

²⁸³ MHRA written evidence to the Review – CSM Minutes August 1974.

²⁸⁴ MHRA written evidence to the Review – CSM Minutes September 1974.

²⁸⁵ MHRA written evidence to the Review – MC 76/112A ‘A Note on Epilim – Sodium Valproate’ 1976.

²⁸⁶ MHRA written evidence to the Review – MC 76/112A ‘A Note on Epilim – Sodium Valproate’ 1976.

²⁸⁷ FD 23/2660 National Archives.

²⁸⁸ A. Richens. Outline proposal for the Medical Research Council on Adverse Effects of Antiepileptic Drugs. AC 77/6. Paper for the MRC Working Party on Anticonvulsant Drugs 17 November 1977.

researchers.²⁸⁹ It expressed concern that *“it was still not certain how well [sodium valproate] compared with other drugs currently in use”*, without specific reference to teratogenicity.

- 4.33 A Steering Group for Trials on Anticonvulsants in Epilepsy was run between 1979 and 1984. This oversaw two trials of efficacy and safety of commonly used antiepileptic drugs in children and adults, but the trials struggled with recruitment,²⁹⁰ the design was questioned by the MRC, and funding was cut in 1984, leading to the trials being disbanded.²⁹¹ Another MRC Working Party on Clinical Research into Epilepsy was established in 1989. This identified *‘pregnancy and “foetal factors”’* as one of several areas of priority for clinical research.²⁹² A paper presented by Dr David Chadwick highlighted the *“particular need for large-scale epidemiologically-based research into the incidence of foetal abnormalities in babies born to women with epilepsy, to determine the risk incurred from treatment with anti-epileptic drugs. The relationship of these abnormalities to the occurrence of seizures during pregnancy or genetic links between epilepsy and foetal abnormalities also requires assessment.”*²⁹³ However it is not clear from the archive material what, if any, actions were taken to support research in this area, although Dr Chadwick went on to publish a number of papers on the teratogenicity of antiepileptic drugs (See Annex C).
- 4.34 An investigation of congenital malformations related to all maternal drug treatment was discussed by the CSM in 1980, but DHSS were unable to fund the study and the Adverse Reactions Sub-Committee proposed that this could be carried out as a student elective study. Decisions on this were deferred *‘pending further consideration of the question of funding, and problems of staffing within the secretariat.’*²⁹⁴ A study on maternal drug histories and congenital malformations was run by the CSM with the Office of Population Censuses and Surveys (OPCS) and was noted by the CSM in December 1982.²⁹⁵
- 4.35 In December 1982 the CSM considered two papers on the teratogenicity of sodium valproate, which included reports on teratogenicity from France, various articles in the professional and non-professional press, and data received from the Company (the manufacturer). The Committee agreed with the licensing view that

²⁸⁹ Medical Research Council Circulation. Neurosciences Board: MRC Working Party on Anticonvulsant Drugs. Final Report. March 1978. FD 23/2660 National Archives.

²⁹⁰ National Archives FD 23/3399 Steering Group for Trials on Anticonvulsants in Epilepsy 1982.

²⁹¹ National Archives FD 23/3402 Steering Group for Trials on Anticonvulsants in Epilepsy 1983-1984.

²⁹² National Archives FD 23/3403 Working party on clinical research into epilepsy.

²⁹³ National Archive FD 23/3403 Working Party on Clinical Research into Epilepsy 1989.

²⁹⁴ MHRA written evidence to the Review – CSM Minutes 30 October 1980.

²⁹⁵ MHRA written evidence to the Review – CSM Minutes 16 December 1982.

no formal action was required against the product licences, and did not object to an amendment proposed by the Company that ‘pregnancy should be carefully monitored in women receiving Epilim’. The Committee agreed that an item should be included in ‘Current Problems’ and that there was a need for specific research into the role of anticonvulsant therapy in antiepileptic mothers in increasing the risks of congenital malformations of the foetus.²⁹⁶ In their response to requests for further evidence, the MHRA did not provide any further details of discussions regarding research into this issue by the CSM.

Emerging concerns about the risk of valproate use during pregnancy

- 4.36 Information on the risks of valproate use during pregnancy emerged in the academic literature. From the early 1980s, data suggested an association between sodium valproate exposure in utero, and physical malformations, with the ‘Foetal Valproate Syndrome’ being described in 1984.²⁹⁷ Other case reports from the late 1980s suggested a neurodevelopment effect, although more substantial evidence did not emerge until the early 2000s. A cumulative meta-analysis conducted in 2015 suggested that statistically significant risks could have been identified for: neural tube defects in 1992; genitourinary and musculoskeletal abnormalities (2004); cleft lip and/or palate (2005); and congenital heart defects (2006)²⁹⁸ (See Annex C and Annex F for further information).
- 4.37 These early case reports were significant in drawing attention to the risk. Professor Clayton-Smith discussed the response to her 1995 paper on Foetal Valproate Syndrome²⁹⁹ with us: *‘quite rightly a lot of other people when we drew attention to this said, well anecdotal reports are not a very good level of evidence and you’re seeing a biased subset of children’*.³⁰⁰ This was echoed in editorials from this period, for example, the following in the Lancet in 1988 which raises a number of questions in relation to the data associating valproate use during pregnancy and neural tube defects: *‘Such important findings should be supported by high quality evidence. This is where the story falls apart. None of the main results has been presented in a full paper with discussion of the epidemiological issues essential to interpretation of the data... The prospective studies may be better, but again few details are available...’*

²⁹⁶ MHRA written evidence to the Review – CSM Minutes 16 December 1982.

²⁹⁷ DiLiberti JH et al. ‘The fetal valproate syndrome’ American Journal of Medical Genetics 1984: 19, 5-14 <https://doi.org/10.1002/ajmg.1320190308>

²⁹⁸ Tanoshima M et al ‘Risks of congenital malformations in offspring exposed to valproic acid in utero: A systematic review and cumulative meta-analysis’ Clinical Pharmacology and Therapeutics 2015: 98(4), 417-441 <https://doi.org/10.1002/cpt.158>

²⁹⁹ Clayton-Smith J and Donnai D ‘Fetal valproate syndrome’ Journal of Medical Genetics 1995: 32(9), 724-727 <https://doi.org/10.1136/jmg.32.9.724>

³⁰⁰ OH Dr Bromley, Professor Clayton-Smith and Professor Turnpenny 26th November 2018.

*Congenital malformation registries have been established in many parts of the world for the purpose of detecting new teratogens and local epidemics, often in response to the thalidomide tragedy... However, those concerned have failed to present the adequately thorough, detailed, and convincing data that are necessary for optimum practical action, and have not explored the biological and teratological questions that arise.'*³⁰¹

- 4.38 Publications from this period discuss the difficulty of attributing these risks to a single anticonvulsant, and distinguishing them from confounding effects including: use of other anticonvulsants during pregnancy, the severity of maternal epilepsy, and familial or genetic risk, and how these should be balanced against evidence of risks of untreated epilepsy during pregnancy.³⁰² Many called for further, large-scale, and well planned research. These lessons do not appear to have been learned; a Cochrane Review twenty years after the risks were first highlighted stated that there was still '*little evidence about which specific drugs carry more risk than others to the development of children exposed in utero*' and called for more population based studies to examine the effects of in utero exposure.³⁰³
- 4.39 Large scale long-term studies that are required to assess pregnancy outcomes, are limited by both researcher interest and funding availability.³⁰⁴ The UK Epilepsy and Pregnancy Register was established in 1996, to collect data on structural abnormalities in the children of women with epilepsy managed with or without antiepileptic drugs. The register started as a research project with limited funding, run by a team with other clinical duties, and which relied on voluntary reporting at three months after birth (at this point any major congenital malformations would be known). The registry has approximately 13,000 registrants to date, with enough patients on most available antiepileptic drugs to show statistical significance.³⁰⁵ The registry was not set up to collect data on longer-term health issues or neurodevelopmental delay. However as evidence of these emerged, the registry has worked with other researchers to conduct longer-term follow-up. Other registries were subsequently established in Europe, North America and Australia.
- 4.40 Given the high prevalence, early reporting of neurodevelopmental effects in case reports, and use of a valproate animal model of autism in research in the early

³⁰¹ 'Valproate, spina bifida, and birth defect registries' The Lancet 1988: 332, 1404-1405 [https://doi.org/10.1016/S0140-6736\(88\)90592-2](https://doi.org/10.1016/S0140-6736(88)90592-2)

³⁰² Lindhout D and Meinardi H 'Spina bifida and in-utero exposure to valproate' The Lancet 1984: 324, 396 [https://doi.org/10.1016/s0140-6736\(84\)90557-9](https://doi.org/10.1016/s0140-6736(84)90557-9); CSM Current Problems 'Sodium Valproate (Epilim) and congenital abnormalities' 1983. Number 9.

³⁰³ Adab N et al 'Common antiepileptic drugs in pregnancy in women with epilepsy' Cochrane Database of Systematic Reviews 2004: CD004848 <https://doi.org/10.1002/14651858.CD004848>

³⁰⁴ OH Dr Rebecca Bromley, Professor Jill Clayton-Smith and Professor Peter Turnpenny 26th November 2018.

³⁰⁵ OH UK Epilepsy and Pregnancy Register 14th March 2019.

2000s,³⁰⁶ it is disappointing that it took so long for evidence of neurodevelopment effects to become accepted. Dr Bromley³⁰⁷ suggested the following reasons that this may have occurred:

- Physical outcomes are still the main focus of teratology research and funding.
- Neurodevelopmental outcomes take longer to be observed and are more difficult to collect data on. Information on autism spectrum disorders, and educational outcomes are more likely to be collected, however other effects may require specialist assessment that is not routinely undertaken.
- The impact of neurodevelopmental effects and outcomes were not taken seriously. Dr Bromley told us: *'It is my personal belief that it took regulatory action for the vast majority of neurologists to truly accept the link between fetal valproate exposure and child neurodevelopmental outcome'*.

4.41 In Chapters 1 and 2 we set out what we consider to be the limitations of our past and current post-marketing surveillance system and how it can be improved. Spontaneous reporting by clinicians was not sufficient to raise alarm; by 1982 Labaz had received information on 106 pregnancies in which the mother was taking sodium valproate,³⁰⁸ and by 1989, only 26 reports of babies with spina bifida whose mothers had taken valproate had been reported to the CSM.³⁰⁹

4.42 It is our view that the entire healthcare system was too slow to respond to emerging data, either with warnings, regulatory action, or by commissioning further research. Annex C shows in more detail the requests for, and conversations around, changes to the warnings associated with sodium valproate use in pregnancy between the manufacturer and the MHRA. We have briefly seen above the difficulties in interpreting early data, and that multiple calls were made for further research. These issues are not valproate, or anticonvulsant specific. Data from the US suggests that on average it took 27 years to determine the physical teratological effect of a drug; for neurodevelopmental effects it could be much longer.³¹⁰

³⁰⁶ The valproate animal model of autism spectrum disorder (ASD) was first tested in 1996 (Rodier et al.), and is now one of the most widely used models of ASD in the field. See written evidence from Professor Clayton-Smith and colleagues.

³⁰⁷ Dr Rebecca Bromley written evidence to the Review.

³⁰⁸ Jeavons PM 'Sodium valproate and neural tube defects' The Lancet December 4 1982: 1282-1283 [https://doi.org/10.1016/S0140-6736\(82\)90141-6](https://doi.org/10.1016/S0140-6736(82)90141-6). A total of 106 pregnancies had been reported to Labaz in 1982, Jeavons combined this with other data to report on the prevalence of neural tube defects in this group.

³⁰⁹ Oakeshott P et al 'Valproate and spina bifida' The Lancet 1989: **333**(8638), 611-612 <https://dx.doi.org/10.1136%2Fbmj.298.6683.1300>

³¹⁰ Adam MP et al. 'Evolving knowledge of the teratogenicity of medications in human pregnancy' American Journal of Medical Genetics 2011: 157(3), 175-182 <https://doi.org/10.1002/ajmg.c.30313>

Communicating information about risk to patients

'As a nurse practitioner I always knew Valproate was probably the cause of her problems yet... I was always told it was not the Valproate.'

'My medication was never reviewed, and it was never brought to my attention that becoming pregnant whilst taking Sodium Valproate would present any risk to an unborn child. When I became pregnant, I was referred to an epilepsy nurse who explained very briefly that there may be a possibility that my child may have a cleft palate, hare lip or may be "middle of the road" in terms of learning. She stressed that it was unlikely, but she had to let me know... I feel disappointed and upset that the risks of using Sodium Valproate were not explained or alternatives offered to me prior to becoming pregnant... it was a planned pregnancy so alternatives could have been explored prior to conception.'

'I was never told the risks that the drug can have on the foetus and even when I asked the doctors if it could affect the foetus or my milk when breast feeding I was told that it is perfectly safe to take – nothing to worry about.'

'...I was told that percentage of chance of difficulties was barely above average compared to other pregnancies and that the most likely problem(if any) would be a slight delay in some childhood milestones but that child would go on to lead "perfectly normal life" This as we now know is quite clearly not the case.'

Women who took sodium valproate during pregnancy

4.43 The Review has heard many worrying accounts that the concerns of patients prior to, or during, pregnancy were dismissed by doctors. Many women have told us that if they had known about the risks related to pregnancy, they would have made different decisions regarding their treatment or family planning. A number of suggestions why women were not made aware of the risks emerged from our conversations with those affected, patient campaign groups, experts and organisations, and these are discussed in more detail throughout this chapter:

- Doctors were unaware of the risks and were unable to advise women appropriately.
- The severity of the risk was minimised, or ability to manage the consequences overestimated.
- In balancing the risks and benefits, doctors prioritised the medical treatment of epilepsy.

- Doctors gave advice based on their own assumptions, without involving patients in the decision-making process.
- Uncertainty of who is responsible for pre-conception counselling led to women not receiving this information from their neurologists or general practitioner.

- 4.44 In the 1970s, in line with the practice at the time, information about the potential and actual risk was only included in the datasheet for physicians. No information was shared directly with the patient, relying on communication from prescribing physicians. We can gain some insight into the culture behind this with an exchange from 1973 about a proposed modification to a datasheet for another anticonvulsant, primidone, to include information about teratogenicity (see Annex C). The Main Committee of the CSM were concerned about causing ‘fruitless anxiety’, and the Adverse Reactions Sub-Committee recommended that in order to ensure prescribers were aware, information *‘could be included in all relevant data sheets but not on package inserts so that there would be no danger of patients seeing it.’*³¹¹
- 4.45 Patient Information Leaflets were introduced for Epilim in 1989. Following guidelines set out by the Association of the British Pharmaceutical Industry (ABPI), they did not contain any specific information, on risk, but directed patients to consult their doctor. A summary paper of the Working Party concluded *‘I believe patients should be told a great deal – but not too much’*.³¹² In their written evidence, Sanofi reported there was considerable debate around the level of detail that should be provided, and that doctors were concerned that a generic leaflet listing side-effects, without a doctor present to discuss the interactions between the medication and an individual’s condition, might lead to the patient stopping their medicine or taking it in a different way to the way that was best for them.³¹³
- 4.46 In 1994, legislation came into force which set out what should be included in package leaflets. The patient information leaflet for sodium valproate in 1994 contained information that: women with epilepsy had a slightly higher risk of having a child with an abnormality than other women; women who take Epilim in first three months of pregnancy have a 1% chance of having a baby with spina bifida; this can be detected on screening tests; and taking folate may lower the risk. The way this information was presented did not make it clear that anticonvulsant medications play a role in the increased risk during pregnancy. By not comparing

³¹¹ National Archives BN 116/17 CSM Sub-Committee on Adverse Reactions. Meetings 17.1.1973-21.11.1973.

³¹² Wells FO ‘Patient Information – the Present and the Future’ Journal of the Royal Society of Medicine 1990: 83(5), 300-302 <https://doi.org/10.1177%2F014107689008300507>

³¹³ Sanofi written evidence to the review and Oral Hearing January 18th 2019.

the rate of spina bifida in the children of women taking Epilim with the general population, it was unclear that the risk was higher in this group.

- 4.47 The patient leaflets stressed that it was essential that women discussed these risks with their doctor, gave clear warnings that women should not stop taking their medication suddenly, and from 2005 advised women that they should use effective contraception and consult their doctor before planning their pregnancy. Stronger warnings on pregnancy were included from 2011, and further information introduced following the outcomes of the PRAC.
- 4.48 Annex F shows a side-by-side comparison of the information communicated to doctors (via the datasheet and later SmPC) and patients (via the patient information leaflet) for Epilim. The language used, detail and emphasis of the information differed according to the audience. Some women have commented that the difference in how the information was communicated made the risk seem less severe, and we agree. In the 1990s, there was a shift in information for healthcare professionals towards advising women that screening could identify any major issues, suggesting that decisions – including presumably the decision to abort the foetus with all the distress that would entail – could be made during the pregnancy, rather than prior to it.³¹⁴ In the SmPCs in 2005 there was information on effects on verbal IQ; in contrast, the patient information leaflet warned women that some children might require additional educational support. An acknowledgement of this difference was made by the MHRA:

*‘The women’s experience of what that risk is like every day with a child who’s been affected is in no way mirrored by points on an IQ scale or cohort studies or whatever our databases are showing us’.*³¹⁵

MHRA, written evidence to the Review

- 4.49 Patient groups also believe that further work by the healthcare system and charities should have been done to ensure that patients received this information, such as outreach via media and social media. We acknowledge that relevant organisations have recently increased efforts to reach patients and healthcare practitioners such as via the PPP, and guideline documents put out by professional bodies. However, we agree that the healthcare system could and should have done more earlier.

³¹⁴ ‘Sodium valproate and spina bifida’ Drug and Therapeutics Bulletin 1990: 28, 59 <https://dtb.bmi.com/content/28/15/59>; ‘Neural tube defects associated with sodium valproate and carbamazepine – need for counselling and screening’ Current Problems 1993.

³¹⁵ OH MHRA 27th February 2019.

- 4.50 It is important that accurate up-to-date information is included in the patient information leaflet, and in other reputable sources which patients might access. However, the interaction between an individual and the healthcare professionals is essential in order to provide tailored advice and support. We have heard from a number of individuals, for whom this interaction has failed, and we explore this next.

The role of healthcare professionals

The introduction of sodium valproate

- 4.51 Valproate was welcomed as a new effective drug by doctors when it was licensed. As set out in Annex F, information on the teratogenicity of valproate in animals was included in the datasheet following the granting of the full product licence in 1974. At this time, given concerns about the safety of the existing anticonvulsant drugs, and the impact of epilepsy itself on pregnancy outcome, choices would have been limited regarding the treatment of women of childbearing age.³¹⁶

Warnings about anticonvulsants

- 4.52 In 1973 the CSM sought to draw attention to the teratogenicity of anticonvulsants, without causing panic among patients and doctors, and to avoid the hazards associated with the withdrawal of the drugs.³¹⁷ There was a disagreement between the CSM Main Committee and its subcommittees on how the risk should be publicised.³¹⁸ Steps taken at this time included information in the Chairman's annual letter to doctors, in the Sub-Committee's report on congenital malformations, and a decision that the Chairman should discuss how publicity on the risk could be achieved with the British Medical Association (BMA). Doctors were advised that the risk was *'not sufficient to justify stopping the use of anti-convulsants when they are necessary for the control of epilepsy'*.³¹⁹ The Main Committee decided against requiring a warning in all datasheets, as *'in practice it would be difficult to identify all manufacturers of drugs used for epilepsy'*.³²⁰
- 4.53 Doctors were advised by the British Medical Journal (BMJ) in 1981 that, in the absence of further evidence about teratogenic risks, *'carbamazepine or sodium valproate seems preferable to phenytoin or phenobarbitone as the first choice for*

³¹⁶ OH MHRA 27th February 2019; Written evidence from Professor Clayton-Smith and colleagues.

³¹⁷ MHRA written evidence to the Review – MC 76/112A 'A Note on Epilim – Sodium Valproate' 1976.

³¹⁸ MHRA written evidence to the Review – Minutes of the CSM and CSM/AR from April to September 1973.

³¹⁹ 1973 CSM Annual Letter to Doctors, quoted in MC 76/112A 'A Note on Epilim – Sodium Valproate' 1976.

³²⁰ MHRA written evidence to the Review – Minutes of the CSM/AR, September 1973.

*the treatment of appropriate types of epilepsy in young girls and women in their reproductive years’.*³²¹ Additionally, the BMJ advised that women should not be discouraged from having a child, satisfactory treatment regimens should not be changed if the epilepsy is well controlled, and ‘Doctors should explain to parents that the increased risk is small and that many of the complications are minor or remediable’.³²²

- 4.54 In 1983, the CSM’s ‘Current Problems’ discussed epidemiological surveys reporting an increase in the incidence of congenital malformations in children born to women with epilepsy, and the difficulty of determining whether this increased incidence was linked to epilepsy itself or the treatment. The article included specific risks that had been reported related to valproate, and notes that newer drugs may only appear less hazardous because evidence of hazard has not accumulated.³²³

Specific warnings and information about sodium valproate and pregnancy

- 4.55 Information communicated via the datasheet to doctors continued to reflect concerns about antiepileptic drugs (see Annex F). In 1984, the information was updated to include advice on monitoring and breastfeeding. Information about the specific risk of neural tube defects was not included in the sodium valproate datasheet until 1990, with advice on screening and counselling of patients. Additional information was added to the datasheet, and from 2001, the SmPC over time (see Annex F). In 2003, the guidance warned that the overall rate of malformations was 2-3 times higher than the rate in the general population, and that an association with developmental delay had been observed. This was updated to include impacts on verbal IQ in 2005.
- 4.56 The MHRA were present at a meeting of the EMA Pharmacovigilance Working Party (PhVWP) in July 2005, at which the French Ad Hoc Pregnancy Expert Working group presented their conclusions that a warning should be added to the SmPC for sodium valproate and carbamazepine regarding the risk of developmental delay and autism. This warning was not included in the PhVWP key principles for valproate SmPCs, and as such neither the MHRA nor the Marketing Authorisation Holder were legally obliged to make this change in the UK.³²⁴

³²¹ ‘Teratogenic risks of antiepileptic drugs’ British Medical Journal (Clinical research ed.) 1981: **283**, 515 <https://dx.doi.org/10.1136%2Fbmj.283.6290.515>

³²² *ibid.*

³²³ CSM Current Problems ‘Sodium Valproate (Epilim) and congenital abnormalities’ 1983. Number 9.

³²⁴ MHRA written evidence to the Review.

- 4.57 The following information on autism was included in the French SmPC in 2006 at the request of the French regulatory agency the AFSSAPS³²⁵: *‘Furthermore, a few isolated cases of autism and related disorders have been reported in children exposed to sodium valproate in utero. Additional studies are necessary in order to confirm or disprove all of these results’*.³²⁶ These changes were not made in the UK until 2010, when the SmPC included a ‘special warning’ for women of childbearing potential, and noted that autism spectrum disorders have been reported in children exposed to valproate in utero. In our view in 2005 there was an opportunity for the UK to adopt these warnings regarding autism, although we acknowledge there was no legal obligation to do so.
- 4.58 Patients and patient groups have also raised a concern with us that this change to the UK SmPC did not take place until after the collapse of the legal case. The Review does not have information about what happened during the case. However, given that the application to update the SmPC in the UK to include a warning about autism spectrum disorders had been submitted in April 2009, it is unfortunate that the update was not approved until October 2010 (see Annex C). This is also an example of the long time periods between an application to change the information about a product and its approval by the MHRA. While we recognise the need to ensure information presented in the SmPCs and patient information leaflets are accurate and up-to-date, these delays are missed opportunities to ensure women and their doctors are given all the information necessary to make decisions.
- 4.59 The risk of congenital malformations was updated again in 2012, to state that incidence was approximately 10%. Subsequent changes were in line with the first and second review conducted by the PRAC, and included the special warnings and precautions in 2015, and information on the PPP in 2018.
- 4.60 Advice on dosage and polytherapy since 1977 has recommended that prescribers should aim for optimum control at the lowest possible combined-dosage level, with a maximum dose of 2,500mg daily (see Annex F). Specific information on dosage in pregnancy was not included in the datasheet until 1994. This recommended that monotherapy was preferred, dosage should be reviewed before conception, and the lowest effective dose should be prescribed. Information on divided doses was added in 1998, and the dose-dependent risk of neural tube defects was added in 2003, particularly above 1000mg daily. This advised that divided doses and prolonged release formulas should be used to avoid peak plasma levels. This was updated in 2015 to state that a threshold dose below which no risk exists,

³²⁵ Agence Française de Sécurité Sanitaire des Produits de Santé. In 2012 AFFSAPS became the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) – National Agency for Safety of Medicines and Health Products.

³²⁶ Sanofi written evidence to the Review.

could not be established. Following the launch of the PPP, this advice on dose has remained the same.

- 4.61 The guidelines were updated in 2012,³²⁷ which included specific advice that *‘When prescribing sodium valproate to women and girls of present and future childbearing potential, discuss the possible risk of malformation and neurodevelopmental impairments in an unborn child, particularly with high doses of this antiepileptic drug (AED) or when using as part of polytherapy (1.9.1.10)’*. Updates since then have reflected the actions of the MHRA and available information,³²⁸ and a summary of the NICE guidance and safety advice was published in March 2019.³²⁹
- 4.62 In addition to the information included in the datasheets, the British National Formulary (BNF) and NICE guidance, the MHRA and its precursors made a number of efforts to directly communicate the risk with clinicians, including via bulletins, alerts and reminders (see Annex F). Information was also communicated directly to doctors by the manufacturer (for example in 1989 Sanofi sent copies of the updated datasheet to GPs), and by charities and patient groups. In addition, a number of published research and reviews have drawn attention to the risks, including the Drug and Therapeutics Bulletins published by the BMJ (see Annex F), and consensus guidelines on management of women with epilepsy.³³⁰ We asked all those invited to give evidence to provide a timeline including communication of regulatory and professional guidance to clinicians and patients, however we have not received further examples of actions taken by professional bodies and regulators to minimise risk prior to the PRAC referral in 2013.
- 4.63 Similar information was also available to doctors in this period via professional guidance publications including the BNF (see Annex F) and NICE. NICE published Technology Appraisals in 2004 on the use of newer antiepileptic drugs for epilepsy in adults and children.³³¹ These discussed the possible interaction of some AEDs with oral contraceptives, and the risks in pregnancy, and advised clinicians that these risks and benefits should be discussed with the patient. NICE also drew attention to the unknown risk of new drugs, and the known risk of harm of sodium valproate use during pregnancy. The view of contributing experts was that despite the concerns in the SmPC, sodium valproate may be an appropriate choice for

³²⁷ NICE. CG 137 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2012.

³²⁸ NICE. CG 137 The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2012.; Updated in 2018.

³²⁹ NICE. Valproate in children, young people and adults: summary of NICE guidance and safety advice. 2019.

³³⁰ Delgado-Escueta AV and Janz D ‘Consensus guidelines: preconception counseling, management, and care of the pregnant woman with epilepsy’ *Neurology* 1992: **42**, 149-160.

³³¹ NICE. Technology Appraisal 76 Newer drugs for epilepsy in adults. March 2004.; NICE. Technology Appraisal 79 Newer drugs for epilepsy in children. April 2004.

women with some types of seizures, provided that women had made an informed choice. Clinical Guidelines were released the same year which clearly set out the responsibility of the clinician to give accurate information and counselling, tailored to individual need, to girls and women with epilepsy on contraception, conception, pregnancy, caring for children, breastfeeding and the menopause, *‘in order to enable informed decisions and choice, and to reduce misunderstandings’* (see Annex F).³³²

Risk minimisation: The Quality and Outcomes Framework indicator

- 4.64 A Quality and Outcomes Framework (QOF) indicator for pre-conception counselling for women between the ages of 18-55 on AEDs was introduced in 2011, but retired three years later, against the advice of the NICE advisory committee. Epilepsy Action surveys show that while the indicator was in place, about a third of women had not received information about sodium valproate and pregnancy. This figure rose to almost half following the retirement of the indicator, suggesting that it had some impact in improving awareness.³³³ In addition, the indicator had provided some overview of the degree to which messaging was being passed on to patients; without this there was no formal monitoring. A new Quality Improvement Module on prescribing safety was included in the QOF for 2019/20,³³⁴ which includes valproate and the PPP. However, this is for a single year – **we believe that an indicator on safe prescribing in pregnancy should be introduced for future iterations of the QOF.**

Risk minimisation: The Valproate Toolkit and Pregnancy Prevention Programme

- 4.65 These risk minimisation programmes emerged from two reviews of sodium valproate by the PRAC of the EMA. The first was triggered by a referral from the MHRA in 2013, which requested that the PRAC gave its recommendation on whether new data on teratogenic effect impacts the balance of benefits and risks of valproate in all of its authorised indications and whether marketing authorisations should be maintained, varied, suspended or withdrawn.

³³² NICE. CG20 The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care. 2004.

³³³ Epilepsy Action written evidence to the Review.

³³⁴ <https://www.england.nhs.uk/wp-content/uploads/2019/01/gp-contract-2019.pdf>

- 4.66 This review reported its recommendations in October 2014. It found that the benefit-risk balance of valproate remained favourable, provided that restrictions in pregnancy were strengthened due to the risk of malformations and developmental problems in children exposed. A number of resources were developed by the regulatory authorities and manufacturers, including educational materials for clinicians and patients and launched as a valproate ‘Toolkit’ in the UK in February 2016.³³⁵
- 4.67 Despite these actions, a survey held in October 2016 found that only 20% of women taking sodium valproate knew the risks of valproate exposure in utero.³³⁶ In addition, a consortium of manufacturers of valproate reported to the PRAC that these risk minimisation measures did not appear to have improved prescribing behaviour.³³⁷
- 4.68 Following these reports, the French regulatory authority, the Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), initiated another referral to consider the effectiveness of risk minimisation measures in March 2017. In February 2018, the EMA announced that all female patients must be on the PPP.³³⁸ Additional steps included reducing the pack size to ensure that drugs were dispensed in their own packaging, with the accompanying warnings and patient reminder card.³³⁹ Following the preparation of educational materials, the MHRA communicated this in April 2018.³⁴⁰ Since then, guidance has been issued by professional bodies for valproate use in women and girls in childbearing years,³⁴¹ and which covers specific concerns in psychiatric medicine³⁴² and in female patients under the age of 18.³⁴³

³³⁵ Valproate and risk of abnormal pregnancy outcomes: new communication materials. Drug Safety Update 2016: 9, 1.

³³⁶ Epilepsy Action written evidence. Survey conducted by Epilepsy Action, Epilepsy Society and Young Epilepsy.

³³⁷ Sanofi written evidence – MAH consortium submitted to PRAC: “A joint Drug Utilisation Study (DUS) of valproate and related substances in Europe using database”.

³³⁸ EMA press release ‘PRAC recommends new measures to avoid valproate exposure in pregnancy’ 09/02/2018.

³³⁹ EMA press release ‘PRAC recommends new measures to avoid valproate exposure in pregnancy’ 09/02/2018.

³⁴⁰ ‘Valproate medicines (Epilim▼, Depakote▼): contraindicated in women and girls of childbearing potential unless conditions of Pregnancy Prevention Programme are met’ Drug Safety Update 2018:11, 1.

³⁴¹ Pan-college document ‘Guidance Document on Valproate Use in Women and Girls of Childbearing Years’ 2019.

³⁴² RCPsych ‘Withdrawal of, and alternatives to, valproate-containing medicines in girls and women of childbearing potential who have a psychiatric illness’ 2018.

³⁴³ RCPCH and BPNA ‘Prescribing valproate to female patients under 18 years of age’ 2019.

Effectiveness of the risk minimisation methods

- 4.69 Concerns have been raised about whether messaging had been effective. For example, a series of case reports was published in 1989 about three women on sodium valproate who became pregnant between 1983 and 1986, and who were unaware of the risk, and not offered prenatal diagnosis.³⁴⁴ The authors suggested that general practitioners should review their routine repeat prescriptions to epileptic women of childbearing age, however no action was taken to ensure that practice matched current warnings.
- 4.70 In 1999, a survey was carried out among female members of the British Epilepsy Association which showed that one third of women had not received any advice about pregnancy.³⁴⁵ The Review has not received evidence about any actions taken to improve messaging in this period. A follow-up survey in October 2003 showed that some women were still not receiving information about the treatment during pregnancy.
- 4.71 A survey of 73 patients by INFACT in February 2019 raised concerns about the effectiveness and compliance with the PPP, in particular that women continued to receive medication in white boxes without information leaflets or cards, and had not been counselled by their GPs. A survey by epilepsy charities found that in the period August 2018 to December 2019, 18% of women were unaware of the risks, and approximately 50% had not heard of the PPP (or received the information card or booklet).³⁴⁶
- 4.72 Although the PPP went much further than the Toolkit in ensuring that women were fully informed about the risks of valproate exposure in utero, it is clear that the risk has not been fully minimised. INFACT tell us that there have been approximately 450 pregnancies between April 2018 and October 2019 in women on valproate, where they have not previously received warnings.³⁴⁷ In our oral hearings we received evidence that while there are some areas of good practice, there remain areas where practice needs to improve. For example, some Trusts wrote to psychiatrists with a list of patients who were potentially at risk and required an urgent review.³⁴⁸ The Royal Pharmaceutical Society (RPS) highlighted that although

³⁴⁴ Oakeshott P and Hunt GM 'Valproate and spina bifida' BMJ 1989;298, 1300-1301 <https://dx.doi.org/10.1136%2Fbmj.298.6683.1300>

³⁴⁵ Crawford P and Lee P 'Gender difference in management of epilepsy—what women are hearing' Seizure 1999;8, 135-139 <https://doi.org/10.1053/seiz.1999.0274>

³⁴⁶ Interim results of valproate survey by Epilepsy Action, Young Epilepsy and Epilepsy Society, December 2019. Unpublished.

³⁴⁷ INFACT, direct communication.

³⁴⁸ OH ABN and RCPsych 28th January 2019.

Clinical Commissioning Groups (CCGs) may have written similar letters to GPs, not all GPs had seen it.³⁴⁹ This was reflected in the inspections carried out by the Care Quality Commission (CQC) and the General Pharmaceutical Council (GPhC) who found that although valproate was being managed appropriately on the whole, some women continued to be prescribed and dispensed valproate without the appropriate warnings.³⁵⁰ Duncan Rudkin of the GPhC told us: *‘I think there is a high level of awareness of what should happen. There isn’t necessarily always that confidence that it is happening.’*³⁵¹ These concerns have been, and continue to be, acted upon by the MHRA, working with patient groups and relevant bodies in the healthcare system to ensure the PPP is effectively implemented.

Healthcare professionals have not acted on these guidelines

- 4.73 Despite there being a number of routes by which information about the risk of valproate use during pregnancy was communicated, it is clear that some doctors were not receiving or acting upon this messaging, for example by changing their prescribing practice, counselling women, or more recently following the guidance emerging from the PRAC reviews. We, and those responsible for communicating these risks and guidance, have found the outcome of these actions hugely disappointing.³⁵² In order to improve how risks are responded to in the future it is important for us to understand why simply increasing the availability of information did not lead to changes in practice, and most importantly, did not lead to patients receiving the information they needed to make informed choices about their care.

Information overload and clinician capacity

- 4.74 Studies conducted in 1999 and 2000 showed that readership among doctors of ‘Current Problems in Pharmacovigilance’ had fallen to 27%, and that time pressure and ‘information overload’ was partly to blame.³⁵³ A similar issue has been discussed regarding alerts in the GP and pharmacy systems. It was reported that it can take two years to change a GP system, of which there are several, and 18 months to change a pharmacy system.³⁵⁴ Alert fatigue, including system alerts, paper and electronic materials has been described as an issue by professional

³⁴⁹ OH Royal Pharmaceutical Society 28th January 2019.

³⁵⁰ OH CQC 26th March 2019, OH GMC and GPhC, 10th January 2019.

³⁵¹ OH GMC and GPhC 10th January 2019.

³⁵² OH MHRA 27th February 2019.

³⁵³ <https://www.nao.org.uk/report/safety-quality-efficacy-regulating-medicines-in-the-uk/>

³⁵⁴ OH RPS 28th January 2019.

bodies and regulators.³⁵⁵ Although recall of women on sodium valproate for a medication review formed part of a 2017 Patient Safety Alert,³⁵⁶ GPs may not have the capacity to carry this out.

Roles and responsibilities of healthcare professionals in relation to family planning advice

- 4.75 We have also heard that there has been confusion over the roles and responsibilities of neurologists and general practitioners in ensuring patients are given appropriate counselling regarding contraception and future pregnancies, creating uncertainty over the process. For example, the Association of British Neurologists told us: *'We can't give specialist contraceptive advice, and we have to obviously liaise with the general practitioner or with – sometimes with a specialist gynaecologist, and that's not within our expertise.'*³⁵⁷ The Royal College of General Practitioners (RCGP) explained that if women did not have effective contraception in place, they should be *'referred back to neurologist to get a pregnancy prevention plan in place.'*³⁵⁸ In our view, **a clear process should be agreed to ensure women are able to get appropriate counselling related to their epilepsy treatment and contraceptive choices.**

Professional attitudes

- 4.76 The patient groups have raised concerns that the professions themselves have been slow to respond to emerging risks, prioritising the need to treat epilepsy. Professional bodies have raised legitimate concerns about ensuring patients have access to appropriate treatment, and of the risks of inadequately treated epilepsy.³⁵⁹ Both patients and clinical experts have told us they feel these concerns have led to neurologists being reluctant to consider the adverse effects, to accept the need to prevent further women from becoming pregnant without being aware of the risks, or to fully involve women in decision-making around their care.
- 4.77 We have heard from women who felt that they were not included in the decision-making process. Despite guidance suggesting that a number of factors should be discussed with patients regarding treatment decisions, and these discussions

³⁵⁵ E.g. OH RCGP, GPhC, and RPS; and the CQC Report 'Opening the door to change: NHS safety culture and the need for transformation' 2018.

³⁵⁶ MHRA/NHS I. Patient Safety Alert. Resources to support the safety of girls and women who are being treated with valproate. 6 April 2017. https://improvement.nhs.uk/documents/911/Patient_Safety_Alert_-_Resources_to_support_safe_use_of_valproate.pdf

³⁵⁷ OH ABN and RCPsych 28th January 2019.

³⁵⁸ OH RCGP 23rd January 2019.

³⁵⁹ ABN written evidence – letters dated October 28th 2014, and 9th December 2014; EMA Public Hearing on valproate: Written Interventions 2 October 2017.

documented,³⁶⁰ patients have told us that their doctors gave advice based on their own assumptions, for example, that a woman might not want to stop driving for the period of medication switching or withdrawal. These views continued to be reflected in the views of some of the professionals who gave evidence to the EMA in 2017.³⁶¹

Assurance

- 4.78 It is our view that regulators and professional bodies should have been more proactive in monitoring whether doctors were aware of guidelines and were following them. Other than the short-lived QOF indicator, information on this has mostly come from surveys conducted by charities and patient campaign groups. We were greatly concerned to hear that professionals and regulators were unclear about where ultimate responsibility lies in the system for ensuring that advice is being followed. During our oral hearings we discussed what issues they perceived there being in the implementation of guidance, and how they saw their own role, and that of others, in assurance.
- 4.79 We heard from the RCGP that although they can use a number of routes to raise awareness among their members (such as newsletters and online modules), they have no means of regulating or checking compliance.³⁶² A new Quality Improvement Module on prescribing safety was included in the QOF for 2019/20,³⁶³ which includes valproate and the PPP. One solution put forward by the RCGP, which could link to this, is an audit of prescribing practices in women of childbearing age with epilepsy to be run as a quality improvement activity as part of the new GP contract.³⁶⁴ Additionally, the RCPsych suggested that similar reviews could be run by relevant Trusts commissioning Psychiatric and Neurological services.³⁶⁵
- 4.80 The GPhC, the professional regulator of pharmacists, shared the actions that had been taken since it had been invited to work with MHRA on this issue in 2018, including through direct contact, and adding assurance about valproate dispensing in GPhC inspections of pharmacies.³⁶⁶ An audit of the provision of advice in

³⁶⁰ 'Withdrawing antiepileptic drugs' Drug and Therapeutics Bulletin 1989:27, 29.

³⁶¹ EMA Public Hearing on valproate: Written Interventions 2 October 2017 https://www.ema.europa.eu/en/documents/other/public-hearing-valproate-written-interventions_en.pdf

³⁶² OH RCGP 23rd January 2019.

³⁶³ <https://www.england.nhs.uk/wp-content/uploads/2019/01/gp-contract-2019.pdf>

³⁶⁴ OH RCGP 23rd January 2019.

³⁶⁵ OH ABN and RCPsych 28th January 2019.

³⁶⁶ OH GMC and GPCH 10th Jan 2019.

this group was also added to the new Pharmacy Quality Scheme,³⁶⁷ part of the Community Pharmacy Contractual Framework. The CQC have also started to focus on valproate in their inspection of general practices since 2018.³⁶⁸

- 4.81 The GPhC discussed with us the difficulty of ensuring that information is being communicated in the most effective way, and the problems of having to disseminate information via a variety of alternative channels, such as pharmacy owners, those responsible for governance, and involving non-registered staff such as counter assistants in the process.³⁶⁹
- 4.82 Guidance issued, including NICE guidelines, have been appropriate to the known risks and alternatives. We recognise that guidelines are advisory, but in our view, more should have been done to ensure that healthcare professionals were aware of and following guidelines. In theory, regulators and professional organisations (such as the CQC, GMC and medical defence unions) reinforce their use through their professional standards and inspection or accreditation processes,³⁷⁰ and this is discussed further in the overarching themes chapter (see Chapter 2, Theme 8 ‘Holding to Account’ Guidelines and Quality paragraphs 2.68 – 2.74).
- 4.83 The patient campaign groups have been instrumental in bringing the lack of compliance with risk minimisation methods to the attention of the MHRA. The MHRA have expressed frustration that a year after the implementation of the PPP, progress has not been made everywhere. They have enlisted the support of chief medical officers and chief pharmaceutical officers, Royal Colleges and other professional bodies, and issued alerts themselves and encouraged these partners to do so.³⁷¹ They have also worked with the CQC and the GPhC to ensure that regulatory measures are being taken into account. In paragraphs 4.93 – 4.99 we discuss further steps to consider to ensure that all women taking sodium valproate have access to appropriate counselling prior to becoming pregnant.

Recognition and Justice

- 4.84 We have focussed so far on the emergence of knowledge of risk about sodium valproate, how this was communicated to healthcare professionals and women taking the drug, and the barriers to this. The patient groups have been crucial in raising awareness of this issue. Between the licensing of valproate, and the MHRA

³⁶⁷ <https://www.gov.uk/government/publications/community-pharmacy-contractual-framework-2019-to-2024>

³⁶⁸ OH CQC 26th March 2019.

³⁶⁹ OH GMC and GPCH 10th Jan 2019.

³⁷⁰ OH NICE 14th February 2019.

³⁷¹ OH MHRA 27th February 2019.

referral to the PRAC, these groups organised themselves, lobbied Parliament, and started a major legal case.

Parliament

- 4.85 The needs of those with epilepsy has been raised frequently in Parliament. These have covered issues such as: provision of epilepsy services; availability of specialist staff, particularly epilepsy nurses; challenging stigma; research for epilepsy treatments; and the risks of antiepileptic drugs during pregnancy. In addition, a number of significant reviews took place (see Annex F), which focussed on improvement of services for people with epilepsy. The risks of valproate use during pregnancy was first raised in Parliament in 1983, and multiple times since (see Annex F). In particular, an announcement was made in the House of Commons in 1995, on a programme of co-ordinated initiatives on epilepsy.³⁷² The Department of Health stated that it would be seeking to raise awareness of foetal valproate syndrome among general practitioners and primary care teams. In our Call for Evidence we asked for any historic actions, however the Department of Health and Social Care did not provide any information on these actions as part of its written evidence to the Review.

Litigation

'We have lost our battle today and the Government is telling us that it wasn't the drugs company's fault. One day my daughter will grow up and ask me what happened – and I will have to tell her that it wasn't the fault of the drugs company, it wasn't the fault of the Government, it wasn't the fault of the doctor...it wasn't my fault. The only person left is her...'

Parent involved in the legal action³⁷³

- 4.86 One route by which affected families have attempted to gain recognition and support from the system is through litigation. Initial claims were brought against NHS Resolution (then known as NHS Litigation Authority) in the 1990s by women and children alleging that exposure to sodium valproate in utero had caused damage. The women claimed that they had not been warned of the teratogenic effects of sodium valproate or given information regarding alternative

³⁷² Hansard 24th October 1995. Volume 264 Column 563. Epilepsy <http://bit.ly/2urp9NI>

³⁷³ Leigh Day written evidence to the Review on behalf of OACS Charity and FACSaware.

anticonvulsants. However, advice received by the NHS Resolution lawyers was that at the point at which many women were prescribed sodium valproate, it was not widely known that it should not be used as a first-line treatment in women of childbearing age.³⁷⁴

- 4.87 Following this, NHS Resolution gave advice to the claimants' legal team and to the Legal Services Commission (LSC, now the Legal Aid Agency), that they would have a better chance of success against the manufacturers.³⁷⁵ Claims were brought against Sanofi Synthelabo from 2004, funded by the LSC, and known as the 'FAC Litigation'. This consisted of the individual claims of over 100 children.³⁷⁶ However, the process was halted in June 2006 due to the withdrawal of legal aid. This was challenged through a judicial review, and legal aid restored, only for it to be withdrawn again in October 2010, a few weeks before the trial was due to start.³⁷⁷ Our understanding is that the Legal Services Commission received legal advice that the claim was unlikely to succeed, and was therefore unable to support the claim any further.³⁷⁸ This was hugely disappointing to the affected families, and although the story was covered in the press,³⁷⁹ and in Parliament,³⁸⁰ further legal action was not taken.

The French Scheme

- 4.88 A public fund was set up by the French Government to provide compensation to those who have suffered one or more malformations or development disorders as a consequence of the prescription of valproate or one of its derivatives during pregnancy prior to 31 December 2015.³⁸¹ The scheme is managed by the National Compensation Board for Medical Accidents (ONIAM), a body responsible for the provision of compensation, including to patients suffering from known side-effects of certain medicinal products in cases where no fault could be proven. A recent reminder was published that children, or the parents or legal representatives of these children can file a claim with ONIAM. There is also an intention to write to all relevant patients to inform them of the scheme.³⁸² €10m was allocated to the

³⁷⁴ NHS Resolution written evidence to the Review.

³⁷⁵ NHS Resolution written evidence to the Review.

³⁷⁶ Leigh Day written evidence to the Review on behalf of OACS Charity and FACSaware.

³⁷⁷ Sanofi written evidence to the Review.

³⁷⁸ Sanofi written evidence to the Review; FACSaware written evidence to the Review.

³⁷⁹ E.g. 'The Epilim case shows the flaws in the legal aid regime' Guardian 29 November 2010; 'Families denied legal aid for epilepsy drug court case' BBC News 8 November 2010.

³⁸⁰ Hansard 17th November 2010 'Withdrawal of legal aid for epilepsy drug court case' EDM #1035; 30th November 2010 (Lords) Volume 722 'Provision of Epilepsy Services' <http://bit.ly/2NVtxvc>

³⁸¹ More detail on the scheme can be found on the website <https://www.oniam.fr/valproate>

³⁸² <https://www.service-public.fr/particuliers/actualites/A13678>

scheme from public funds in 2017 and €70m in 2018. Sanofi do not contribute to the scheme,³⁸³ but have said that they will accept any responsibility attributed to it by a court.³⁸⁴ In February 2020, prosecutors in France launched an investigation into the marketing of Depakine (sodium valproate).

Conclusions

4.89 We have listened to the views of those affected and involved in this issue. We are aware that sodium valproate use spans over 40 years, and that the culture in medicine, including the role of the patient, and the nature of their relationship with healthcare professionals and the health system, has changed. It is not the intention of the Review to judge the actions of the past by the standards of today. However, it is our view that, as data emerged on the risks of the use of sodium valproate over the decades, it took too long for action to be taken by the healthcare system to ensure that risks were minimised. Women should have been warned, even if there were no alternatives, so that they could be better prepared. Our more general recommendations can be found in Chapters 1 and 2. Here we discuss the areas for improvement that are specific to sodium valproate.

Information gathering

4.90 Not all of those affected by exposure to sodium valproate in utero have been identified or formally diagnosed. This means that there are some affected who may not be accessing the care and support they need. **Information should be collected to identify those already exposed to ensure they have access to diagnosis, and to plan service provision.** An initiative from the centre using nationwide prescribing information to trace women and their children could assist with this and we have already taken steps to drive this forward.

4.91 **We also want to see a registry for all women on antiepileptic drugs who become pregnant, to include mandatory reporting of data relating to them and their child(ren) collated over lifetimes. This should not be limited to sodium valproate but should include all antiepileptic drugs.** We have heard from patients and experts who are concerned that the long-term outcomes of the newer generation drugs are unknown. They point to how there were little concerns about valproate effects during pregnancy when it was first licenced, and that they do not want to see history repeated. For example Dr Jim Morrow raised concerns about the lack

³⁸³ Sanofi written evidence to the Review.

³⁸⁴ 'Sanofi will accept epilepsy drug blame if court rules that way' Reuters October 27 2016 <https://www.reuters.com/article/us-sanofi-epilepsy/sanofi-will-accept-epilepsy-drug-blame-if-court-rules-that-way-idUSKCN12R28B>

of long-term data relating to neurodevelopmental risk of topiramate exposure in utero.³⁸⁵ We are aware that the Commission for Human Medicines (CHM) is currently considering all AEDs and congenital malformations and would expect the outcome of this review to influence the development of this registry.

- 4.92 This registry could potentially be expanded to collect data on paternal and transgenerational effects (i.e. effects in children of those who were exposed to valproate in utero), both issues which have been raised by those affected as being of great concern. Although a theoretical route of transgenerational effects in animal studies has been suggested, there is no evidence of this in humans.³⁸⁶ Further research into this was recommended by the PRAC following their review of available evidence.³⁸⁷

Ensuring all women have relevant information for decision-making around pregnancy, and reducing exposure to risk

- 4.93 It is clear that the actions taken to date have failed to ensure that no woman becomes pregnant without being aware of the risks of valproate use during pregnancy. A recommendation to undertake systematic identification of all girls and women who are taking valproate, and to provide them with the appropriate resources to make decisions about their medication, was sent out by the MHRA and NHS Improvement in 2017.³⁸⁸ However, not all GP practices have invited all women and girls on valproate for a medication review. It is essential that this takes place as there remain women who are not aware of these risks.
- 4.94 It is our view that **the relevant stakeholders should continue to work with patient groups to monitor and improve the PPP and to consider the next steps.** We recognise that there are a number of practical and ethical considerations around valproate use and the PPP. For example, a recent report suggested only half of at-risk patients taking valproate were physically present in the pharmacy to collect medication,³⁸⁹ and we have heard from women who were concerned that they would not be able to access their preferred treatment due to being unwilling to use long-term contraception for personal or religious reasons. Guidance on any

³⁸⁵ OH UK Epilepsy and Pregnancy Register 14th March 2019.

³⁸⁶ OH Dr Frances Elmslie 10th January 2019.

³⁸⁷ EMA 'Assessment report: Medicinal products containing substances related to valproate' 2018.

³⁸⁸ MHRA/NHSI. Patient Safety Alert: Resources to support the safety of girls and women who are being treated with valproate. 6 April 2017.

³⁸⁹ Company Chemists' Association. Valproate medicines safety in community pharmacy. <https://thecca.org.uk/wp-content/uploads/2019/11/Valproate-safety-audit-report.pdf>

further steps should be clear on how these should be delivered to more vulnerable individuals or those with more complex needs.³⁹⁰

- 4.95 All women currently on sodium valproate should be contacted for a medication review. This should be happening as part of the PPP but we are aware that it has not happened in all cases. All women on valproate should be sent a letter from a body at the centre of the system, copied to their GP, informing them that if they are on valproate they should have had an annual review, been given information leaflets to take away with them, and signed the Annual Acknowledgement of Risk form. If this has not taken place, they should contact their GP or specialist and arrange an appointment. NHS England and NHS Improvement (NHSE&I) should collect information from GPs on whether the form has been signed within the previous year. It is particularly important for women who choose to remain on valproate without contraception, or while pregnant, that conversations around risk, and the decision taken by the patient with their specialist, are fully recorded on the Acknowledgement of Risk form.
- 4.96 NHS England considered that relevant organisations of the healthcare system had acted appropriately in relation to the PPP. They raised the question – what goes beyond issuing a safety alert?³⁹¹ NHSE&I agree that contacting women directly is the next step, and we have discussed progress on this action with them and with the MHRA. The MHRA are working with NHS Digital to develop a valproate registry to monitor the PPP, but are concerned that the timeframes are too long, and do not meet the urgency of the situation. NHS Digital are able to extract a dataset of women on valproate in each GP practice in England, which should allow a letter to be sent to each GP with the names of patients who need to be reviewed. The MHRA informed us that they are following this up with NHSE&I who would be responsible for this action. We have stepped in to press NHSE&I to take action from the centre to ensure every woman of childbearing age on valproate is contacted directly, and a letter copied to their GP, for this vital conversation to take place. We understand that systems are in place to enable this to be feasible, and NHSE&I is investigating next steps. We wish to reiterate the urgency of the need to contact women directly in this way.

³⁹⁰ For example, the current Pan-College Guidance sets out how healthcare professionals should manage the care of those women who choose to remain on valproate without a PPP (page 15-16) and in patients with intellectual disability (page 16-17). Guidance from the British Paediatric Neurology Association and the Royal College of Paediatrics and Child Health sets out how the Prevent strategy might apply to female patients in different age groups under the age of 18.

³⁹¹ OH NHS England 14th February 2019.

4.97 We recommend the following steps:

- **NHSE&I to write directly to all women and girls of childbearing potential, asking them to see their general practitioner or specialist. This letter should be copied to the GP.**
- **An online system for the PPP is considered, which includes confirmation that the Risk Acknowledgement Form has been signed within the previous year. This could be accessed by pharmacists at the point of dispensing.**

4.98 If these steps are unsuccessful, the following suggestions have also been made to the Review as ‘last resort’ measures. These carry higher risks, for example, they have implications for access to essential medications, or would require increased contact with specialists (when we are aware that many women are struggling to access a neurologist), and would need to be considered in far greater detail before any implementation.

- Make valproate only available through specialist prescribing
- Make valproate a controlled substance
- Remove the indication for valproate, so that all prescribing would be ‘off-label’

4.99 There has been a reduction in valproate prescribing in female patients in all age groups in England between January – March 2018 and July – September 2019.³⁹² The UK has a higher rate of valproate prescribing than many other countries in Europe. For example Denmark has roughly 20% of the UK’s estimated patient years for treatment.³⁹³ This suggests that the number of female patients on valproate in the UK (for any indication) could be further reduced. **We would expect clinicians to continue to follow guidance regarding prescribing of valproate and alternatives for all indications.**

Meeting needs of those affected

4.100 **Specialist centres should be established for all families affected by teratogenic medication, to provide integrated medical and social care expertise to enable those affected to access the services they need in one place (Chapter 1, Recommendation 5).** This would allow a single place for diagnosis, including genetic testing, and to co-ordinate referrals. When establishing these centres, it

³⁹² Prescribing for Sodium Valproate. NHS BSA Prescription Data. <https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/sodium-valproate>

³⁹³ MHRA written evidence to the Review.

should be considered how they can work with existing child development units and local services. These centres should be responsible to carry out and publish research, including on long-term outcomes.

4.101 It should be for the experts at these centres to decide on the specific services offered, but suggestions we have received from patients, patient groups and clinicians include:

- Provision of support at home, school or in the community.
- An annual health assessment for those with FVSD diagnosis.
- A health ‘passport’ – developed with input from patient groups to convey essential patient information to relevant agencies. A version of this has been developed by the patient group community (shared at the stakeholder meeting), and summary sheets for patients, parents, health care practitioners, educators and psychologists were included as part of the consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability.³⁹⁴

4.102 **An *ex gratia* scheme to provide discretionary payments should be established (Chapter 1, Recommendation 4).** These payments are to supplement current health and social care provisions, not to replace them. Eligibility should be based on avoidable harm occurring after in utero exposure to valproate. We cannot make recommendations on compensation, which remains the preserve of the courts. Nothing can undo the harm that has been done to these individuals, but steps can be taken to make their lives easier. This scheme should provide practical needs-based help with the additional costs that FVSD incurs.

4.103 We have not seen evidence of specific failures by Sanofi to act within the regulatory framework in place at the time. However, in our view merely complying with the minimum requirements is not enough; for example, it was the patient groups that suggested using a pictogram to warn about the risks of use during pregnancy. There remains a question as to the extent to which the manufacturer should take some ethical responsibility for the harms caused by patients taking sodium valproate during pregnancy. FACSaware argue: *‘Those exposed [to sodium valproate in utero] have lifelong disabilities and have been unable to access justice in the UK courts. The services required by those affected and their families are highly specialised.*

³⁹⁴ Clayton-Smith J et al ‘Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability’ Orphanet Journal of Rare Diseases 2019;14, 180 <https://doi.org/10.1186/s13023-019-1064-y>

*The taxpayer is paying for the services required and the pharmaceutical industry is not contributing.*³⁹⁵

- 4.104 In light of what is said above, in our view Sanofi have an ethical obligation to contribute to the scheme set out in the paragraph above.

Preventing future harm

- 4.105 We consider that the MHRA and CHM should establish a consistent policy on prevention of risk exposure during pregnancy. While it is understandable that there are ethical barriers to testing of medications in pregnancy, there is often insufficient monitoring of long-term outcomes of medications which are necessary during pregnancy (for example for the management of long-term conditions such as diabetes). This lack of good quality evidence for decision making prevents women and their supporting health care professionals from being able to make informed decisions about treatment and family planning. Recently there have been advances to improve this evidence. The MHRA is working on improving safety of medicines use in pregnancy.³⁹⁶ Additionally, a five-year grant was awarded to the ConcePTION project, which is working across Europe to build a system to generate, monitor and disseminate information on the safety of medicines use in pregnancy and breastfeeding.³⁹⁷
- 4.106 We support the efforts to improve our knowledge of risks of medicines use in pregnancy. The case of valproate demonstrates that even where there is some awareness of risk, this is not always effectively communicated to women. **A system similar to the Pregnancy Prevention Programme should be used where teratogenicity is well-known or the effects are severe. Alternatively an acknowledgement of risk form should be attached to the prescribing and dispensing of all medication considered to have teratogenic potential or known to have a risk above that of the general population.**

³⁹⁵ FACSaware written evidence to the Review.

³⁹⁶ <https://www.gov.uk/government/news/mhra-and-the-bill-melinda-gates-foundation-to-look-at-the-safer-effective-use-of-medicines-during-pregnancy>

³⁹⁷ More information can be found on their website: <https://www.imi-conception.eu/>

- Sodium valproate was known to be teratogenic in animals at the time of licensing. Despite this, no long-term follow-up was conducted at that time.
- As concerns emerged about the risk of congenital malformations and neurodevelopmental effects warnings given to patients lagged behind that given to doctors.
- Many women were not given enough information about the risks and benefits of their epilepsy treatment and family planning options to make fully informed decisions.
- It took over 40 years for the healthcare system to put into place measures to ensure that women were fully informed of the risk prior to becoming pregnant.
- The Pregnancy Prevention Programme (PPP) sets out the conditions under which all girls and women of childbearing potential should be treated with valproate. Despite these measures, hundreds of women are still becoming pregnant on valproate while unaware of the risks.
- An apology is due, and support is required for those who have suffered avoidable harm.
- Those affected are not receiving adequate support. We recommend that specialist centres are established for all families affected by teratogenic medication, to provide integrated medical and social care expertise to enable those affected to access the services they need in one place.
- We have discussed with NHSE&I that all women and girls of childbearing potential are written to, asking them to see their general practitioner or specialist to ensure they are receiving treatment in line with the PPP.
- We also make recommendations to reduce the risk of exposure to suspected or known teratogens.

Actions for Improvement	
An indicator on safe prescribing in pregnancy should be introduced for future iterations of the QOF.	4.64
In our view, a clear process should be agreed to ensure women are able to get appropriate counselling related to their epilepsy treatment and contraceptive choices.	4.75
Information should be collected to identify those already affected by exposure to valproate in utero to ensure they have access to diagnosis and support, and to plan service provision.	4.90
A prospective registry should be established for all women on antiepileptic drugs who become pregnant, to include mandatory reporting of data relating to them and their child(ren) collated over lifetimes. This registry could potentially be expanded to collect data on paternal and transgenerational effects.	4.91 – 4.92
The relevant stakeholders should continue to work with patient groups to monitor and improve the PPP and to consider the next steps, which should include NHSE&I writing directly to all women and girls of childbearing potential, asking them to see their general practitioner or specialist.	4.94 – 4.97
Clinicians should continue to follow guidance regarding prescribing of valproate and alternatives for all indications.	4.99
See Chapter 1, Recommendation 5	4.100 – 4.101
See Chapter 1, Recommendation 4	4.102 – 4.104
A system similar to the Pregnancy Prevention Programme (PPP) where teratogenicity is well-known or the effects are severe. Alternatively an acknowledgement of risk form should be attached to the prescribing and/or dispensing of all medication considered to have teratogenic potential or known to have a risk above that of the general population.	4.106

5 Pelvic Mesh

'This device took everything from me my health my life my job my dignity my marriage my freedom. There are a lot of us suffering.'

A mesh-affected patient

Introduction and Summary

- 5.1 Pelvic mesh has been inserted during surgery to support pelvic organ prolapse (POP) and to treat stress urinary incontinence (SUI). For many women mesh surgery is trouble-free and leads to improvements in their condition. However, this is not the case for all. There is no reliable information on the true number of women who have suffered complications. While they may be in the minority, that does not diminish the catastrophic nature of their suffering or the importance of providing support to them and learning from what has happened to them.

Pelvic Mesh can be used for Pelvic Organ Prolapse and Stress Urinary Incontinence.

Pelvic Organ Prolapse (POP) describes a variety of conditions that occur when one or more pelvic organs drop out of their normal position, often pushing into the vagina, causing a bulge. The bladder can push into the front, or anterior, wall of the vagina causing a prolapse (a cystocele). The rectum can push into the back, or posterior, wall of the vagina causing a prolapse (a rectocele). The uterus, or if the woman has had a hysterectomy the vaginal vault, can prolapse downwards into the vagina. In more severe cases prolapses can protrude out of the vaginal opening.

Stress Urinary Incontinence (SUI) is the involuntary leaking of urine when the bladder is under pressure. SUI can be caused when the pelvic tissues, ligaments and muscles, which support the bladder and urethra, are weakened or damaged so that the sphincter that closes the urethra fails when under pressure, and urine leaks out.

During surgery mesh can either be inserted through an incision in the vagina (transvaginal insertion) or through an incision in the abdomen (abdominal insertion).

- 5.2 Women with mesh implants have told us of severe and chronic pain, infections, reduced mobility, sexual difficulties, autoimmune issues and psychological strain. The outcome data that exists currently does not capture all reported symptoms, hence complication rates are not fully understood.

Adverse events following pelvic mesh surgery:

- **pain**; sometimes severe and chronic; we have heard from women with severe pain who require strong opioid painkillers just to function and who can neither stand nor sit comfortably;
- **recurrent infections**; women have described living in fear of antibiotic resistance;
- **mobility issues**; in some cases due to nerve damage; women have described how restricted their lives are now, some rely on crutches or are confined to a wheelchair;
- **recurring or new incontinence/urinary frequency**;
- **recurring or new prolapse**;
- **haemorrhage**;
- **bowel issues**; including fistula formation, offensive discharge, difficulty defaecating, constipation, in some cases colostomy and ileostomy surgery;
- **erosion of mesh**; this can be into the vagina and/or other organs;
- **sexual difficulties**; including pain on intercourse and a loss of sex life;
- **autoimmune issues**; including fatigue, 'brain fog', skin complaints, hair loss, and swelling;
- **psychological impacts**; including depression, anxiety and Post-traumatic Stress Disorder, social withdrawal, suicidal feelings, attempted suicide;
- **death**; mesh complications have been implicated in the death of at least one patient in the UK.

Mesh complications also lead to: relationship and family breakdown, loss of employment, loss of a home, financial hardship.

Listening to those affected – ‘Our Review will listen, learn and recommend.’

- 5.3 It was patients themselves, and the support groups they have established, who raised the alarm about mesh complications, both the scale and the severity. It has been patient groups who have highlighted the lack of reliable and complete data on outcomes and risks from pelvic mesh procedures. And they have shone a light on the inadequate aftercare for those suffering complications. It is they who have highlighted systemic failures in our healthcare system.
- 5.4 Our focus was on listening to those affected by complications, and we met or had contact in writing and by phone with many hundreds. Every woman’s story is unique, but each is sad and deeply moving. Many are fearful of what their future holds. Yet they are brave and dignified, as well as understandably angry, in the face of such adversity. Their tenacity and knowledge of the issues is remarkable. The fact they have had to fight to be heard and to be taken seriously, adds insult and a sense of injustice to injury.
- 5.5 Few of the women who have a successful mesh insertion without complications contacted us. We also know there are some women who are keen for mesh surgery for the treatment of SUI to be resumed (see below). We know this is an imbalance. However, our Review has been focussed on those who have suffered, as set out in our Terms of Reference.

Restrictions on pelvic mesh surgery

- 5.6 Over the past decade concerns about transvaginal³⁹⁸ POP mesh have led to increased restrictions both in the UK and abroad. In 2011 the Food and Drug Administration (FDA)³⁹⁹ concluded that ‘*serious adverse events are NOT rare*’ in transvaginal POP mesh repairs. In response the Medicines and Healthcare products Regulatory Agency (MHRA) commissioned the 2012 York report⁴⁰⁰ and published

³⁹⁸ An incision site in the abdomen is cleaned pre-operatively with an antiseptic agent, the vagina is not disinfected, and is sometimes referred to as a ‘clean contaminated’ site.

³⁹⁹ Public Health Notification: Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Transvaginal Placement for Pelvic Organ Prolapse (13 July 2011), available at <http://www.fda.gov/downloads/MedicalDevices/Safety/AlertsandNotices/UCM262760.pdf>

⁴⁰⁰ J. Mahon, M. Cikalo, D. Varley, J. Glanville, *Medicines and Healthcare Products Regulatory Agency – Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse – Final Report*, York Health Economics Consortium (2012).

their own 2014 Summary paper.⁴⁰¹ These reports concluded mesh for SUI was safe, but caution was needed when using transvaginal POP mesh. The 2015 European Union (EU) Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) Opinion⁴⁰² found similarly – transvaginal POP repair should only be considered in complex cases where non-mesh repair had failed. In 2017 the Scottish Transvaginal Mesh Implants Independent Review⁴⁰³ recommended stopping transvaginal POP mesh surgery. National Institute for Health and Care Excellence (NICE) guidance was promptly changed, and since then transvaginal POP mesh surgery has been restricted to research trials only.⁴⁰⁴

- 5.7 In July 2018, concerned by the stories we had already heard from women who have suffered, we recommended a pause in mesh procedures for SUI.⁴⁰⁵ We did so because we felt that women were being exposed to the risk of life-changing injuries and measures were urgently needed to mitigate these risks. Our recommendation was immediately accepted by NHS England and the Department of Health & Social Care (DHSC), and the pause was implemented. It allowed for the use of mesh to treat SUI only in prescribed exceptional circumstances and under high vigilance. SUI mesh procedures rapidly declined from July 2018.⁴⁰⁶
- 5.8 The conditions that would need to be satisfied before a lifting of the pause could be considered were:
 - i. Surgeons should only undertake operations for SUI if they are appropriately trained, and only if they undertake operations regularly;
 - ii. They report every operation to a national database;
 - iii. A register of operations is maintained to ensure every procedure is notified and the woman identified who has undergone the surgery;

⁴⁰¹ MHRA *A summary of the evidence on the benefits and risks of vaginal mesh implants* 28 October 2014 Available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/402162/Summary_of_the_evidence_on_the_benefits_and_risks_of_vaginal_mesh_implants.pdf

⁴⁰² Scientific Committee on Emerging and Newly Identified Health Risks, 2015, *Opinion on the safety of surgical meshes used in urogynecological surgery*, available at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_049.pdf

⁴⁰³ *The Scottish Independent Review of the use, safety and efficacy of transvaginal mesh implants in the treatment of Stress Urinary Incontinence and Pelvic Organ Prolapse in women Final Report* Final Report March 2017 <http://www.gov.scot/Resource/0051/00515856.pdf>

⁴⁰⁴ 2017 NICE (UK) Guidance IPG59913.

⁴⁰⁵ IMMDS press release and NHS E/I letter dated 9 July 2018 <https://www.england.nhs.uk/2018/07/provider-bulletin-11-july-2018>

⁴⁰⁶ We have been monitoring the use of synthetic mesh for SUI surgery since the pause and only a handful of synthetic mesh SUI operations have been carried out. Up to date numbers can be found here <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-episode-statistics-for-admitted-patient-care-outpatient-and-emergency-data>

- iv. Reporting of complications via the MHRA is linked to the register;
- v. Identification and accreditation of specialist centres for SUI mesh procedures, for removal procedures and other aspects of care for those adversely affected by surgical mesh;
- vi. NICE guidelines on the use of mesh for SUI are published.⁴⁰⁷

All these conditions had been suggested by others before us, but never implemented.⁴⁰⁸

- 5.9 These conditions had three purposes. Firstly, to mitigate the risks associated with surgeons with insufficient skills. Secondly, to develop an accurate record of women undergoing mesh procedures and any associated complications to establish the true risks. This will enable women to make informed choices about treatments. Thirdly, to ensure appropriate care and support for those suffering mesh complications.
- 5.10 Now, almost two years later, we know little more about the nature and extent of mesh associated complications than when the pause was implemented. We have discussed with NHS Digital a retrospective audit and follow-up of women who had pelvic mesh surgery in 2010. We anticipate this will constitute a representative sample providing far greater detail on mesh complications in the decade after surgery. Every effort should be made to obtain sufficient data, and the audit results (assuming it is feasible) should be used to inform decisions over the future of pelvic mesh surgery.

Should pelvic mesh use be banned?

- 5.11 We have considered whether it would be right to recommend a complete ban on the use of mesh in SUI surgery. We acknowledge that there may be some women with specific clinical needs for whom mesh is the only appropriate option. But those women must be able to make a fully-informed decision based on clear and unbiased information – the benefits, the risks, the alternatives, and doing nothing. A woman who has made an informed decision on that basis is one for whom treatment is appropriate. We also firmly believe that mesh use should be

⁴⁰⁷ NICE published guidance NG123 in April 2019 <https://www.nice.org.uk/guidance/ng123>

⁴⁰⁸ For example NICE Technology Assessment Tension-Free Vaginal Tape for Stress Incontinence, TA56 <https://www.nice.org.uk/guidance/ta56/documents/final-appraisal-determination-tension-free-vaginal-tape-gynecare-tvt-for-stress-incontinence2>; The Mesh Oversight Group Final Report (27 July 2017) <https://www.england.nhs.uk/wp-content/uploads/2017/07/mesh-oversight-group-report.pdf>; the letter from Sir Bruce Keogh and Prof. Keith Willett to NHS Medical Directors on 21 November 2012 VAGINAL TAPES AND MESHES available at https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/213189/Vaginal-tapes-and-meshes-letter-to-NHS-final1.pdf as well as various research publications.

considered as a last-line option after conservative non-surgical options, and after consideration of non-mesh surgery. On this basis we anticipate that the number of women choosing mesh SUI surgery in future will be low. The conditions attached to the pause have not yet been met. It will be important for NICE to update their guidance as new information on outcomes becomes available, potentially including the results of the retrospective audit we describe in paragraph 5.10.

Specialist centres for mesh complications

- 5.12 Care for those who have suffered is essential. Current provision is hard to access and variable. Our recommendations include establishing centres that provide specialist care for mesh-injured women (**Chapter 1, Recommendation 5**). Prior to publication of this report we held a series of discussions with NHS England about the specification for these services. The commissioning of the centres is in progress under NHS England's specialised commissioning framework. These centres will need to be able to remove mesh, where that is possible, and provide other services for women with complications. Specialist centres could also serve as the hub to inform clinical networks relating to the use of mesh for SUI and POP. These clinical networks should have a specific responsibility to facilitate research.
- 5.13 However, we have concerns over mesh removal services:
- i. There is currently no consensus among specialist surgeons over the relative risks and benefits of full and partial mesh removal, or which techniques and approaches should be offered, and hence over what is best for each woman. NICE is silent on these matters.
 - ii. Outcome data, especially long-term data, for mesh removals is lacking so we do not know the success or complication rates.
 - iii. The lack of surgeons able to carry out full mesh removals, particularly for mesh that runs through the obturator foramen, creates a skills gap.
 - iv. Consent to mesh removal surgery may not always be fully informed.⁴⁰⁹

Unless these issues can be rectified both the pace and process of accreditation of the specialist centres will be hindered. The Royal Colleges, professional associations and specialist clinicians here in the UK urgently need to collaborate with each other and international colleagues to share outcome data and to reach a clinical

⁴⁰⁹ IMMDS *Our concern over partial mesh removals* (13 December 2019) <http://immdsreview.org.uk/news.html>

consensus on mesh removals. Surgeons need to be clear with women about the nature of the procedures they are able to carry out, the technique they intend to use, and possible risks or complications.

The database

- 5.14 A fully-functioning database that will capture every mesh implant and removal is required (**Chapter 1, Recommendation 7**). Following mandation by the Secretary of State in November 2019 good progress has been made by NHS Digital. In future women who agree to take part in research will be identified from the database and will become part of a registry. The registries will need to use validated Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) to provide much needed and long-awaited data on the relative risks and benefits of different pelvic mesh procedures and different devices.

Background

The use of pelvic mesh

- 5.15 Since the 1950s mesh has been used to provide support for tissue repair. Flat mesh sheets were cut to fit, and used for many purposes including hernia repair and vascular repairs.

Mesh can be made from a variety of materials (synthetic and biological) and created in variety of ways: weaving, spinning and more recently electro-spinning. Synthetic meshes can be made from a wide range of polymers. Polypropylene is the most commonly used for synthetic mesh, but other polymers are available. For example we heard oral evidence from FEG Textiltechnik mbH* who make polyvinylidene difluoride (PVDF) pelvic meshes. Natural materials, such as collagen, can also be used. Meshes may be impregnated with other substances, for example oestrogen.

Mesh structures vary. Historically mesh could be made from fibres that are composed of one filament (monofilament meshes) or fibres that are made up of multiple fibres (multifilament meshes). The size of the gaps or 'pores' between the mesh strands is used to characterise synthetic meshes. Meshes with gaps of $>75\text{ }\mu\text{m}$ are known as 'macroporous', whereas those $<10\text{ }\mu\text{m}$ are 'microporous'. The $75\text{ }\mu\text{m}$ pore size is important as immune cells, fibroblasts, blood vessels and collagen fibres cannot pass through smaller gaps, which can lead to poorer clinical outcomes. Now pelvic surgery only uses type 1 (monofilament macroporous) synthetic mesh.

*OH FEG Textiltechnik 23rd January 2019.

- 5.16 Our remit was to examine the use of mesh to support pelvic organs.⁴¹⁰ The two main conditions where mesh is used to support pelvic organs are POP and SUI. We have considered POP and SUI separately as they involve different operations that use mesh in different ways with different reported complication rates. We have included both abdominally-inserted and vaginally-inserted POP mesh.

Pelvic Organ Prolapse (POP) surgery

- 5.17 POP symptoms vary. Some prolapses do not cause any issues, others can have a significant impact. Symptoms include a feeling of dragging or of a lump in the vagina; a more general feeling of dragging or heaviness in the lower abdomen; a bulge or lump protruding from the vagina; discomfort or alterations in sensation during sex; problems with passing urine, including urinating frequently, inability to fully empty the bladder and SUI.
- 5.18 Conservative treatments for POP can involve specialist pelvic floor physiotherapy, pessaries, and lifestyle and behavioural changes, such as losing weight, and the use of protective pads or clothing. Non-mesh surgical options for POP are also available and the choice of surgery will depend upon the location and extent of the prolapse and outcomes vary accordingly, (see Annex G Pelvic mesh supporting information).
- 5.19 Mesh has been used to support POP for many years. Initially flat mesh was cut by the surgeon to fit each individual woman. From the early 2000s kits comprising pre-cut, pre-shaped mesh, supplied with or without custom applicators, were developed.⁴¹¹
- 5.20 Mesh (synthetic and biologic) can be used for rectal prolapse and for a rectocele in a procedure known as a ventral mesh rectopexy (VMR). External rectal prolapse occurs when the rectum, the lowest part of the bowel, protrudes through or out of the anus. During a ventral mesh rectopexy the rectum is returned to its correct position, and is secured in place using mesh, which is stitched to the rectum and fixed to the sacrum.

Stress Urinary Incontinence (SUI) surgery

- 5.21 SUI varies in severity. In mild cases, leaking only occurs with pressure from sudden forceful activities, such as exercise, sneezing or laughing. In severe SUI the pressure

⁴¹⁰ When hernia mesh is used in the pelvic area it is used to support the cavity wall, usually the abdominal wall, rather than to support pelvic organs so it is not within our terms of reference. However, we recognise that the composition of the meshes used in hernia and POP surgery is often indistinguishable, and therefore we trust that, where relevant, our recommendations will have read-across.

⁴¹¹ For example, on 8 Jan 2002 FDA clearance of gynaemesh for POP (K013718). In the mid 2000s mesh kits were developed for POP mesh.

needed to cause a leak is lower, and can be caused by everyday activities such as standing up or walking. Leaks range from a few drops to enough to soak clothes.

- 5.22 Conservative non-surgical treatments can be successful for many women with SUI and include among other options specialist pelvic floor physiotherapy, pessaries, maintaining a normal body mass index (BMI), urethral bulking injections, medications and coping strategies such as using protective pads. Pelvic floor physiotherapy after childbirth is particularly important (see paragraph 5.123).
- 5.23 Before the advent of surgical mesh, the most commonly performed operation for SUI was a colposuspension. This operation was popularised in the early 1960s and aimed to hitch the bladder neck upwards and provide support for it. A support for the bladder neck is made by securing the lower front part of the vagina to the ligament behind the pubic bone using two stitches, one on either side of the bladder neck. Open surgery colposuspensions are major operations that are done under general anaesthetic and require several days' inpatient stay in hospital. Laproscopic colposuspensions were found to be as effective as open colposuspensions in a Cochrane review in 2006, but were superseded by mesh operations.⁴¹²
- 5.24 In the 1960s surgeons started to use an inlay or 'sling' to support the bladder neck in cases of severe SUI. These 'slings' could be autologous (made from the patient's own tissue), cadaverous (tissue from an organ donor donated after death) or from mesh (synthetic or biologic). The use of cadaverous tissue declined after fears over the transmission of diseases but autologous and mesh surgery are still used.⁴¹³
- 5.25 From 1996 kits for SUI became available in the United States,⁴¹⁴ and by 1998 the tension-free vaginal tape (TVT) was available in the UK.⁴¹⁵ The number of TVT operations rose dramatically – and by 2001, just three years after its launch, the

⁴¹² Bezerra CCB, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD001754. <http://dx.doi.org/10.1002/14651858.CD001754.pub2>

⁴¹³ Mesh surgery is currently heavily restricted under the pause and can only be carried out under a 'high vigilance' regime. For more detail see appendix A of the Letter from Prof Stephen Powis and Dr Kathy McLean to Regional Directors, Trust Medical Directors, and clinicians involved in the care of patients with stress urinary incontinence and pelvic organ prolapse, 2019, EXTENSION OF PAUSE TO THE USE OF VAGINAL MESH, available at: https://improvement.nhs.uk/documents/5122/MESH_letter_-_Extension_of_pause_on_the_use_of_vaginal_mesh_29_March_2019.pdf

⁴¹⁴ The first commercially available SUI kit was Boston Scientific's ProteGen sling, which was cleared by the FDA in November 1996. It comprised a synthetic Polyester sling and was voluntarily recalled in 1999 due to higher than anticipated rates of erosion and wound dehiscence (when a wound spontaneously reopens along the surgical incision).

⁴¹⁵ Ethicon written evidence to the IMMDS Review. The TVT marketed in UK from 1998. Ethicon details of TVT.

TVT was the most commonly performed operation for SUI in the UK.⁴¹⁶ The TVT was modified into transobturator tapes, such as Mentor's ObTape and Ethicon's TVT-O, in an attempt to reduce bladder perforations. Further modifications led to single incision and Mini-slings.

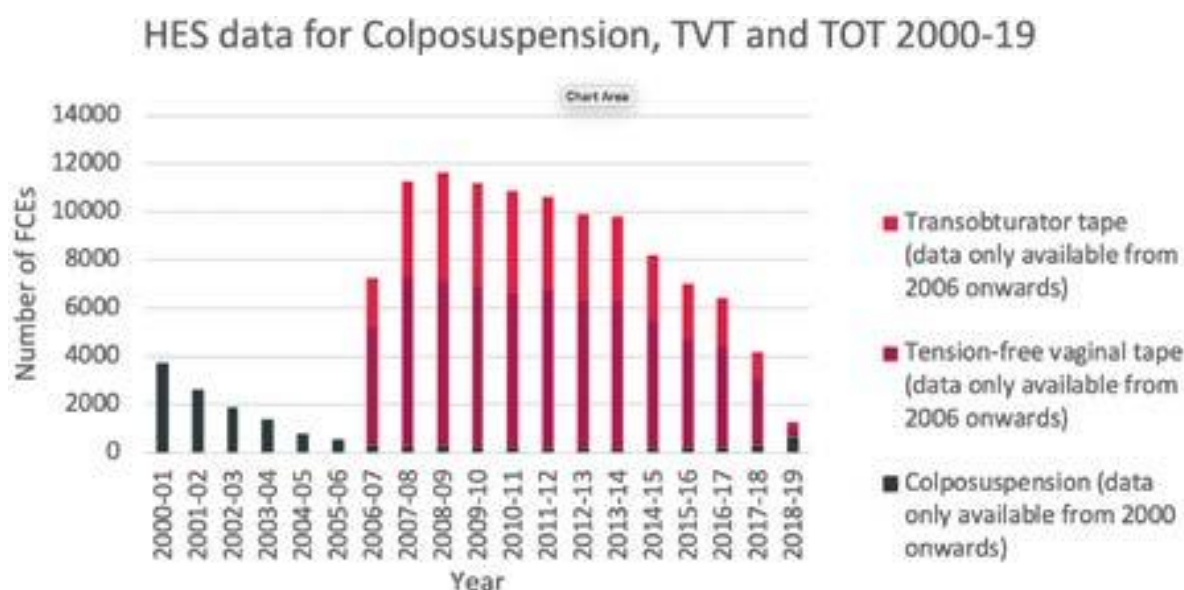
Numbers of pelvic mesh operations performed

- 5.26 In England in-patient activity is listed in Hospital Episode Statistics (HES).⁴¹⁷ HES records the number of care 'episodes' rather than how many patients have been cared for.⁴¹⁸ A procedure can only be accurately recorded in HES data once it has been allocated an OPCS code, but the allocation of a code often lags many years behind the procedure coming into use. Colposuspension of the neck of the bladder was allocated a code in 2000-2001. Tension-free vaginal tape and transobturator tapes were only allocated their codes in 2006-2007.
- 5.27 Graph 5.1 shows the number of colposuspensions and insertions of each type of tape recorded in HES data from 2000 to 2019. This data is incomplete as it only covers NHS procedures, but it illustrates how mesh surgery replaced and exceeded colposuspensions, only to decline similarly as mesh complications and the publicity surrounding them began to surface. The rapid uptake of mesh surgery also calls into question just how many more women underwent mesh surgery whose condition would not have previously been considered severe enough to merit a surgical intervention.

⁴¹⁶ Ward KL, Hilton P; UK and Ireland TVT Trial Group. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. *BJOG*. 2008;115(2):226–233. <http://dx.doi.org/10.1111/j.1471-0528.2007.01548.x>

⁴¹⁷ All procedures in NHS hospitals are coded using OPCS codes. These codes were originally devised by the Office of Population Censuses and Surveys (OPCS) for the NHS. They have been refined and added since then.

⁴¹⁸ Hospital Episode Statistics (HES) is a database containing details of all admissions, A and E attendances and outpatient appointments at NHS hospitals in England, see <https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics>



Graph 5.1 HES data for Colposuspensions, TVT and TOT insertions 2000-2019

Concerns about mesh surgery

The suitability of synthetic mesh for use in the pelvic region

- 5.28 We sought expert advice on whether synthetic mesh is inherently suitable for insertion into the pelvic region.⁴¹⁹ The experts discussed with us the composition and form of the device, the skill of surgeon, and any predisposing factors the patient has. Throughout the Review we heard differing opinions among experts. We did not find a consensus that synthetic mesh is inherently suitable or unsuitable for use in the pelvic region. We did find agreement that meshes with a larger surface area, such as POP meshes, provide greater potential for foreign body reaction and inflammatory immune responses than smaller meshes, such as those used for SUI.
- 5.29 Another contentious area is whether mesh shrinks and/or stretches while in the pelvic region. Surgeons have told us that mesh can shrink and stretch.⁴²⁰ In their written evidence to us Ethicon state *‘the mesh in Ethicon’s TVT and POP devices itself does not shrink. Instead, the macroporous Ethicon meshes allow for the integration of the patient’s tissue through the mesh (by design) which naturally forms scar tissue. During wound healing and scar formation, the tissues may contract whether or not mesh is present.’*⁴²¹ Again, we did not find a consensus.

⁴¹⁹ Properties of mesh teleconference.

⁴²⁰ OH BSUG/PFS 16th April 2019.

⁴²¹ Question 9 of Ethicon’s written evidence to the IMMDS Review.

- 5.30 The properties of pelvic mesh may change once it is implanted in the body.⁴²² Using mesh to support pelvic organs puts the mesh under tension or ‘loading force’. Even a mild loading force can reduce pore size, increasing the risk of adverse effects.⁴²³
- 5.31 The experts we consulted agreed that mesh will degrade, or oxidise, if it is exposed to the air and so mesh exposure requires treatment.⁴²⁴ They agreed that the outer edges of mesh fibres can degrade when it is inside the body. However, there was no agreement on the implications of degradation when mesh is in the pelvis; some experts we consulted were of the view this was clinically significant, others were not.
- 5.32 A highly contentious issue is leaching of chemicals from the mesh and potential systemic reactions to this, including immune and autoimmune disorders. Views appear to be polarised on this, and we cannot find a consensus from the available scientific literature on possible leaching, and any clinical implications.
- 5.33 **Further research is urgently needed in all these areas so that a clearer view can be reached on the inherent properties and safety of pelvic mesh.** Other materials and manufacturing techniques are being researched in an attempt to improve the efficacy and safety of synthetic materials used in this area.⁴²⁵

What are the adverse effects of mesh? – ‘This is not a life. It is an existence’.

‘This is not a life. It is an existence. With potentially another 40 years ahead... this is a depressing prospect.’

Mesh-affected woman

- 5.34 Some adverse effects of mesh are immediately obvious, and as soon as they recover from the anaesthetic women have realised something has gone wrong. Other issues

⁴²² Mancuso, E, Downey, C, Doxford-Hook, E, Bryant, MG, Culmer, P. The use of polymeric meshes for pelvic organ prolapse: Current concepts, challenges, and future perspectives. *J Biomed Mater Res.* 2019; 1– 19. <https://doi.org/10.1002/jbm.b.34432> and Taylor, D & Barton, E. In vitro characterisation of the erosion of soft tissues by surgical mesh, *J Mech Behav Biomed*, 101 (2020) 103420 <https://doi.org/10.1016/j.jmbbm.2019.103420>

⁴²³ Paragraph 484 of Gill v Ethicon Sàrl (No 5) [2019] FCA 1905 ‘For mesh strips, even a mild loading of 1N [one newton] has a dramatic impact on the resulting pores size as far as soft meshes like Ultrapro are concerned. Under this loading the initial pore size of between 3–4 mm decreases to values down to 0.3mm.’ available at <https://www.judgments.fedcourt.gov.au/judgments/judgments/fca/single/2019/2019fca1905>

⁴²⁴ Properties of mesh teleconference.

⁴²⁵ For example, see Mancuso E et al. (as above); evidence from FEG Textiltechnik to the Review.

only become apparent much later; some women experience no complications until years after the procedure. However, not all women suffer adverse effects following mesh implantation. For some women mesh surgery appears to be complication free.

- 5.35 In the recent Australian class action case,⁴²⁶ Ethicon's expert witness Dr Hinoul conceded that, from the time of first supply Ethicon was aware,⁴²⁷

'...that a foreign body reaction to surrounding tissue would create a scar, that the mesh could be subjected to a contracting force applied by surrounding scar tissue, that the response of the host tissue was variable, and that any significant degree of contraction could lead to pain as could the scarring itself.'

'...there was a risk of mesh exposure into the vaginal canal or another organ, that mesh exposure could be difficult to treat, and that it could cause pain or discomfort.'

'...that both mesh erosion and pain could occur many years after devices had been implanted.'

'...that implantation carried a lifelong risk of erosion and pain, as well as risks of: dyspareunia and, as a consequence, apareunia; difficulty voiding; difficulty defecating; offensive discharge; leg weakness; and damage to surrounding organs, ligaments, tissues, and blood vessels.'

- 5.36 Non-mesh surgery can also result in these same adverse events, with the exception of erosion. The issue at the heart of the Australian litigation was the magnitude and gravity of the risks of mesh surgery and the extent to which a manufacturer was obliged to disclose them. It was conceded by Ethicon that at the point of first supply they knew *'both acute and chronic pain could be caused by each of the devices, that chronic pain could be very damaging and debilitating, indeed "life-altering", and that multiple operations might be necessary to attempt to alleviate the pain.'*⁴²⁸
- 5.37 Mesh inserts are intended to become permanently embedded into the surrounding tissue, making removal complex.⁴²⁹ Common sense dictates that if an implantable device is known to be difficult, perhaps impossible, to remove, then it should only be used where there is a pressing medical need that could not be met by

⁴²⁶ Note that Ethicon have stated that they intend to appeal against the judgment in this case.

⁴²⁷ Paragraphs 189 – 191 Gill v Ethicon Sàrl (No 5) [2019] FCA 1905 available at <https://www.judgments.fedcourt.gov.au/judgments/Judgments/fca/single/2019/2019fca1905> were

⁴²⁸ Paragraph 190 of Gill v Ethicon Sàrl (No 5) [2019] FCA 1905 available at <https://www.judgments.fedcourt.gov.au/judgments/Judgments/fca/single/2019/2019fca1905>

⁴²⁹ Some biological meshes are intended to dissolve, so will disappear over time.

conservative treatment. Sadly, this approach has not always been applied to pelvic mesh surgery.

- 5.38 From the point that mesh was first marketed it was acknowledged that serious adverse events could occur, see paragraph 5.35. It took until 2015 for Ethicon to include information on their SUI mesh products that removal of implanted mesh might be difficult. Even then no information was given as to how removal might be undertaken.⁴³⁰ In our view **if a manufacturer recognises that their product may cause severe complications, they and others, such as the regulators, must develop a remedial strategy for dealing with these complications and set this out in the Instructions for Use (IFUs) and guidance.**

Recognition of adverse outcomes, including patient-reported outcomes

‘So I went back to the consultant to discuss things, Unfortunately he is very pro mesh and when I asked if he thought my issues were linked to my TVT-O he actually screamed at me “you need to stop listening to the media and those bloody women, I fit hundreds of these every year and you’re only person I’ve seen who is complaining and thinking you have problems.’

Mesh-affected woman

- 5.39 The lack of listening to mesh-injured women has been recognised. In 2017 in his foreword to NHS England’s Mesh Oversight Group’s Final Report⁴³¹ Professor Keith Willett recognised, *‘These women felt their concerns had been ignored.’* Time and time again women told us that those conducting follow-up research only asked about selected outcomes, often only surgical outcomes. For example, in following up SUI surgery, they asked about continence. Objective surgical outcomes are vital, but so are patient-reported outcomes. The women tell us that questions were not asked about other important outcomes, such as pain or sexual functioning. Information on risks and complications is incomplete and not representative.
- 5.40 The published literature on mesh tends to focus on short-term surgical outcomes and robust PROMs have generally not been sought. The conventional sources of information for doctors – published articles, regulatory information, professional society communications – did not accurately reflect the outcomes women were

⁴³⁰ Paragraphs 2900 – 2901 Gill v Ethicon Sàrl (No 5) [2019] FCA 1905 available at <https://www.judgments.fedcourt.gov.au/judgments/Judgments/fca/single/2019/2019fca1905>

⁴³¹ Mesh Oversight Group Report, July 2017, available at: <https://www.england.nhs.uk/publication/mesh-oversight-group-report/>

experiencing. The published evidence available gave the medical profession little cause for concern about mesh or information about the full range of mesh complication. Doctors who are unaware of the risks of mesh are less likely to recognise women presenting with mesh complications. This is a cycle: while doctors do not recognise complications and/or attribute them to mesh then professional awareness remains low and as a result doctors are more likely to fail to correctly identify mesh complications.

‘How can the benefits outweigh the risks? I understand that SUI is sometimes debilitating and distressing, but I can assure these injuries are negatively life changing beyond words.’

Mesh-injured woman

- 5.41 The MHRA has maintained that the benefits of SUI mesh and abdominally inserted POP mesh outweigh the risks, as set out in their 2014 report produced at the request of the Chief Medical Officer (CMO).⁴³² In their guidance NICE have consistently stated that pelvic mesh should remain available, that the benefits outweigh the risks.⁴³³ In our view such a stance does not fully reflect an understanding of all the risks. As we have outlined above, adverse outcomes are not always reported in the medical literature. As Michelle Moffatt from Sling the Mesh told us:

‘There is no evidence to inform long-term safety and the real-world evidence and patient stories of harms have been overlooked.’⁴³⁴

- 5.42 Some mesh-injured women have described their surgeon in positive terms, even when the surgeon cannot resolve their mesh-related complications. We know there are some excellent surgeons doing their best to care for mesh-injured women, but one mesh-injured woman emailed *‘my journey to find a surgeon who believed that my current health situation is down to mesh complications has been like traipsing through treacle.’* We have also heard from women whose doctors,

⁴³² MHRA, A summary of the evidence on the benefits and risks of vaginal mesh implants, 28 October 2014, available at: <https://www.gov.uk/government/publications/vaginal-mesh-implants-summary-of-benefits-and-risks>.

⁴³³ NICE has classified all pelvic mesh procedures as ‘standard arrangements’, ‘special arrangements’ or ‘research only’. These place various restrictions on the use of the product/procedure, but do not say it must not be used. A “Special Arrangements” recommendation does not imply the procedure should be restricted or should not be used. The most restrictive category, Research only, places strict conditions on when a product/procedure can be used, but is not a ban on use. Annex G Pelvic Mesh Supporting Information describes the NICE guidance at the time of publication.

⁴³⁴ OH Sling the Mesh 21 May 2019.

surgeons and GPs ignored or dismissed their concerns. *‘One thing we’re hearing a lot, especially in women of a certain age is that they are told that their symptoms are probably due to their menopause. That is being repeated over and over again. Now it implies a distinctive apathy within the profession that they could think that.’* Yvette Greenway, Mashed up by Mesh.⁴³⁵ The dismissive, defensive and arrogant attitude that so many women told us they encountered from their surgeon when reporting post-surgical problems was a persistent theme throughout our Review. *‘I feel that I have been lied to, and not taken seriously. I felt completely let down by the way I have been treated and unable to prove what I know is the truth.’* Mesh-injured woman

- 5.43 We have also heard from mesh-injured women who were categorically told by their doctors that their problems could not be caused by their mesh, despite a second opinion proving otherwise. *‘They would tell you there was nothing wrong with you and that you were just a hysterical woman. I came up against all this.’* Teresa Hughes, Meshies UK.⁴³⁶ We have also been told of missing or altered medical records. Women have confided in us their concerns about deliberate cover ups, and have shown us medical notes that appear to have been amended.
- 5.44 We have also heard that some hospital Trusts routinely destroy medical notes a set number of years after a patient has last visited the hospital. This is concerning for long latency issues such as mesh adverse events where the harm may not become apparent for many years. The move from paper to digital hospital records should resolve this issue.

Identifying women with mesh complications

- 5.45 Mesh complications can occur many years after the initial surgery. This makes attribution far more difficult, particularly if the woman herself may not know that she had mesh inserted and her doctor, often her GP, may also be unaware.
- 5.46 We still have insufficient understanding of mesh complications. To date there is no comprehensive registry and few long-term studies, hence our recommendations about the need for a database and linked registries (see Chapter 1).

How many women are affected? – Data on mesh complication rates.

- 5.47 There is a lack of clarity on the number of women who have had mesh surgery. Although we have an idea of the scale of the problem from the experimental

⁴³⁵ OH Mashed up by Mesh 21 November 2018.

⁴³⁶ OH Meshies United Group UK 21 November 2018.

audit⁴³⁷ done by NHS Digital, we know that this data is incomplete. It also only covers NHS operations not private procedures. The data relies on HES codes, the creation of a HES code lags behind the operations, often by several years, and may contain errors. The denominator (the number of women who have had mesh inserted) is therefore unclear.

- 5.48 We also have limited information on the proportion of women who will suffer complications related to the mesh insert. We do not believe that current published data reflects either the full range of, or rates of, mesh complications.
- 5.49 The history – and current status – of mesh is such that no one knows this basic and essential information. Among the experts we have spoken to there seems to be little consensus on risk factors for mesh surgery. Some argue that certain factors such as pre-existing autoimmune conditions increase the likelihood of adverse outcomes.⁴³⁸
- 5.50 There are limitations in the safety and outcomes data collected on mesh. The initial safety data used when launching the products onto the market relied on short-term studies with limited, or no, long-term follow-up. Given what we now know, that mesh complications can arise many years after insertion, this was seriously remiss. With the benefit of hindsight, it seems foolhardy to implant a product that is meant to be a permanent implant into so many women with such paucity of long-term data. New permanent implants should be introduced far more cautiously, potentially using cohort studies with extensive long-term follow up (**Chapter 1, Recommendation 6**) and with a comprehensive database to allow tracing of each individual with that implant (**Chapter 1, Recommendation 7**).

Why were so many SUI meshes inserted? The 'gold standard' operation

'She suggested that it was such an easy fix, that it was almost unthinkable that I would have any other options.'

Mesh-injured woman

- 5.51 The perception that mesh was a quick easy fix for SUI meant surgeons carried out mesh operations on women who would not previously have been considered for

⁴³⁷ This audit is experimental because HES data is designed to record how many treatments took place, not how many patients were treated. This is the first time any data set has been analysed using a pseudo-anonymised patient identifier to try to determine how many people were treated.

⁴³⁸ Paragraphs 278 – 298 *Gill v Ethicon Sàrl* (No 5) [2019] FCA 1905 available at <https://www.judgments.fedcourt.gov.au/judgments/Judgments/fca/single/2019/2019fca1905>

surgery and the volume of surgical procedures increased significantly. Many of the women we met told us that their surgeon had referred to the mesh procedure as the new ‘gold standard’, a phrase that appears to have been used by so many surgeons in so many parts of the country that it could be no coincidence.⁴³⁹ Mesh was presented as the ‘gold standard’ for resolving SUI when the risks of it were unascertained.

- 5.52 We recognise that some risks of new treatment options may only become apparent when they have been in use for some time, and that surgeons need to be able to offer new, innovative treatments. As initially happened in the case of mesh, adverse events caused by a device are not always attributed to the device. **In clinical trials of medicines all adverse events (regardless of cause) are reported. Had selected cohorts of early device users undergone this type of enhanced reporting, it might have highlighted the incidence of serious complications such as severe chronic pain and sexual difficulties much earlier.** However, enhanced reporting during early trials would not have detected longer latency issues that we know have occurred.
- 5.53 Inserting a mesh kit was much quicker and easier than the traditional non-mesh SUI surgery, such as colposuspensions. *‘...at the time the training was so minimal, and the knowledge by surgeons was so minimal, and both things are the most important points of this.’* Hayley Martin, TVT Messed Up Mesh.⁴⁴⁰
- 5.54 Trials also report better outcomes,⁴⁴¹ for example the Ward & Hilton paper from 2002⁴⁴² (funded by mesh manufacturer Ethicon)⁴⁴³ reported that the TVT had a slightly higher objective cure rate, a much shorter minimally invasive surgery with a faster recovery time and fewer post-operative complications. The faster recovery and fewer bed days created a financial incentive to offer a TVT in preference to the more complex and time-consuming colposuspension.

⁴³⁹ The Ethicon written evidence to the IMMDS review at paragraph 2.2 states ‘Professional gynecologic and urological societies worldwide have endorsed the biocompatibility of polypropylene and have found full length mid-urethral slings such as the Ethicon TVT and TVT-O devices to be the gold standard treatment option for SUI while the use of macroporous polypropylene has been recognized as the gold standard for apical prolapse.’

⁴⁴⁰ OH TVT Messed up Mesh 21 May 2019.

⁴⁴¹ P. Song, Y. Wen, C. Huang, W. Wang, N. Yuan, Y. Lu, Q. Wang, T. Zhang & J. Wen. The efficacy and safety comparison of surgical treatments for stress urinary incontinence: A network meta-analysis. *Neurourol Urodyn.* 2018 Apr;37(4):1199-1211, Epub 2018 Jan, <http://dx.doi.org/10.1002/nau.23468>.

⁴⁴² K. Ward, P. Hilton, Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ : British Medical Journal* **325**, 67-67 (2002). <https://doi.org/10.1136/bmj.325.7355.67>

⁴⁴³ This paper reported a prospective multi-centre randomised comparison of TVT and colposuspension in 344 women.

The development of mesh for SUI

- 5.55 The TVT Instructions for Use (IFU) indicate that the TVT should be inserted through a small incision. The smaller cut means healing time is reduced. However, surgeons have limited visibility when inserting a TVT, so much so that it has been described to us as operating ‘blind’. In their evidence to us, Ethicon indicated that the TVT-O was developed as a means of avoiding bladder injuries that had been occurring during TVT insertion. The TVT-O was associated with **serious adverse events such as nerve damage, leg pain and mobility issues. In addition, a TVT-O is much harder to remove in its entirety than a TVT. NICE’s most recent guidance states that the TVT-O should not be offered routinely.**⁴⁴⁴ In the future, we feel the TVT-O should only be used in exceptional circumstances, if at all.
- 5.56 The development and use of TVT-Os raises a question mark over whether the modification of a device so that it required less skill to insert should have been the preferred option rather than improving the surgical skill base. Outcomes for patients should be paramount. We have grave concerns over devices being marketed to, and inserted by, less skilled surgeons. **Professional bodies should lead on ensuring surgeons only operate within their capabilities. They must provide guidance for their members and ensure that surgeons are appropriately trained. This training should be assured through the appraisal process.** We wish to see specialist centres which will be hubs of expertise and training (see paragraph 5.100).

Unnecessary operations

‘I was fitted with a TVT-O for stress urinary incontinence. I was a super fit, 42 year old Mum of two, who worked out and swam daily, ran my own business, was chair of a local children’s charity, who suffered the occasional mild leak when jumping. My surgeon told me that he could fix this issue with a quick and easy 20 minute operation that would see me back at work and the gym within a week.’

‘I was never offered any alternative conservative treatment and I was certainly never fully informed of the potential risks.’

Women suffering with mesh complications

⁴⁴⁴ NICE, 2019, Urinary incontinence and pelvic organ prolapse in women: management, available at: <https://www.nice.org.uk/guidance/ng123>

- 5.57 We have heard from women who had mesh surgery to alleviate severe SUI, which was having a significant impact on their quality of life. However, we have also heard from a number of women who underwent mesh surgery for relatively minor SUI, without having first had, or having been offered, conservative treatment, and who are now living with devastating mesh-related complications (see graph 5.1 which clearly shows the upsurge in mesh surgery).
- 5.58 We have heard how Multi-Disciplinary Team (MDT) working is helpful in ensuring balanced, considered decisions. **We agree with NICE that any mesh implantation decisions must involve an MDT.**⁴⁴⁵ **A culture must exist where all MDT members feel able to speak up and that their input will be listened to. MDTs where decisions are dominated by one individual do not serve anyone well. Trusts must work to create a culture that facilitates effective MDTs.**
- 5.59 **Conservative measures must be offered to women before surgery. We are concerned that specialist pelvic floor physiotherapy cannot match the demand; further resource is needed. In our view it is for the service commissioner to identify gaps in the workforce and to notify specialist clinicians, professional organisations and Royal Colleges. A co-ordinated strategy can then be developed to remedy the gap.** In her oral evidence to us Natalie Beswetherick, the Director of Practice and Development of the Chartered Society of Physiotherapy, said ‘We know that the size of the workforce, the specialist workforce, is insufficient to provide pelvic floor muscle training in all those who require it, so current service provision is limited. We’re aware of that – and variable across the NHS in the UK.’

What risks were women told about? Informed consent

‘I honestly do not think that any of these guys [surgeons] realise how bad this stuff is. There is no way anyone would consent to that, would they? Or the fact that you lose your sex life or the fact that you can’t be a mum anymore or that you’re going to need carers. Who would consent to that?’

Candia McCullough, Mesh UK Charitable Trust⁴⁴⁶

- 5.60 **Patients must have sufficient understanding of their treatment,⁴⁴⁷ including the potential risks it presents, and the alternative treatment options, in order to decide whether they are willing to have that treatment.** Mesh surgery was

⁴⁴⁵ NICE Guidance [NG123] ‘Urinary incontinence and pelvic organ prolapse in women: management’ (April 2019) available at <https://www.nice.org.uk/guidance/ng123>

⁴⁴⁶ OH Mesh UK Charitable Trust 21 November 2018.

⁴⁴⁷ There are some exceptions, usually where a patient is unable to make a decision for themselves, some examples are ‘with ‘for example children and people who are unconscious.

almost exclusively elective surgery, which includes a consent process where details of the operation, its risks and likely outcomes, should have been conveyed to the patient. This did not always happen, *‘The only advice/warning I was given about this procedure was that it “may not work”, I was not informed about any possible complications other than anaesthetic-related and that was brief.’*

- 5.61 Consent can only be informed consent when the patient understands both the procedure and the risks. Lack of effective communication deprives patients of their autonomy, and that is wrong and unacceptable. We talk about this and the implication of the *Montgomery* judgement in Chapter 2 on ‘Overarching Themes’, Theme 3.⁴⁴⁸
- 5.62 It is clear to us that some women underwent a pelvic mesh procedure without even knowing that mesh was to be used. The terminology used by surgeons was variable, confusing and sometimes misleading. For example, some women were told their operation involved a repair, but were not appropriately informed that this repair would involve mesh. Some surgeons described using a ‘sling’, ‘tape’, or ‘ribbon’. *‘I was certainly never fully informed of the potential risks. Furthermore this device was described to me as ‘tape’ and not plastic.’* It was not clear to the women these were just alternative words for the same product: mesh.
- 5.63 Patients can only make an informed decision when they have the facts. Effective risk communication involves explaining known risks and complications and also what is unknown about risks and complications. If there is limited information on the risks of a treatment the treating doctor has a duty to tell the patient that there is not enough information to assess the frequency or severity of the risk. In the case of a device intended to be permanently implanted, the doctor must communicate what is known and not known about long-term risks.
- 5.64 Manufacturers must ensure that any information for patients and clinicians must be clear and must accurately reflect what is known. The IFUs for TVT did not contain a warning about dyspareunia *‘Pain with intercourse which in some patients may not resolve’* until 2015, despite Ethicon admitting that they knew of this risk from the point the product was first marketed.⁴⁴⁹ The information given to the patients in the brochure and the information given to clinicians in the IFUs etc must be consistent.
- 5.65 Many women have told us risks were either not mentioned or that the incidence and/or severity of the risks was not made clear *‘...as women who have had these mesh procedures, we don’t feel we were informed properly, given enough*

⁴⁴⁸ *Montgomery v Lanarkshire Health Board* [2015] UKSC 11.

⁴⁴⁹ Paragraph 2879 of Paragraph 484 of *Gill v Ethicon Sàrl* (No 5) [2019] FCA 1905 available at <https://www.judgments.fedcourt.gov.au/judgments/Judgments/fca/single/2019/2019fca1905>

information. I don't know what they're given now but I certainly wasn't told what it was made of and what could happen to me. That was also true of a lot of women that I spoke with, they hadn't been told how they could end up, and weren't given that decision.' Teresa Hughes, Meshies United Group UK.⁴⁵⁰

- 5.66 Leaflets produced by hospital Trusts and the Royal College of Obstetricians and Gynaecologists (RCOG) were used in some cases. Such leaflets have a value, but they are no substitute for proper documented risk communication conversations. On too many occasions leaflets were far from being as clear as they could have been.⁴⁵¹ In future all patient information must be co-designed with patients to ensure clarity and comprehensibility (see Chapter 2, paragraph 2.22).

Better informed consent processes – Patient Decision Aids

- 5.67 We have been impressed by the process of development of the pelvic mesh Patient Decision Aid (PDA) in Ayrshire, Scotland.⁴⁵² This was developed collaboratively with patients and consequently has a focus on understanding the outcomes that matter to the patient and providing clear information to assist with decision making. NICE have subsequently developed their own PDA.⁴⁵³
- 5.68 **Clinicians need to establish and agree terminology and definitions related to both mesh insertions and removals.** Information should be conveyed to patients in a way that is clear and meaningful (see Chapter 2, paragraph 2.21). Patient Decision Aids must use the agreed terms, and need to be collaboratively developed with patients as described in Chapter 2, paragraph 2.22.

SUI Mesh development– objectivity, independence and interests

- 5.69 The initial investigations of the TVT were carried out in Sweden by Professor Ulmsten and were funded by the Swedish Medical Research Council.⁴⁵⁴ He reported a high cure rate with low levels of complications and he then sold the rights to the TVT to Ethicon (a subsidiary of Johnson and Johnson). As part of the due diligence

⁴⁵⁰ OH Meshies United Group UK, 21 November 2019.

⁴⁵¹ Sling the Mesh written evidence to the IMMDS Review.

⁴⁵² H. L. Ong *et al.*, Development, validation and initial evaluation of patient-decision aid (SUI-PDA©) for women considering stress urinary incontinence surgery. *International Urogynecology Journal*, (2019). <http://dx.doi.org/10.1007/s00192-019-04047-z>

⁴⁵³ NICE, 2019, Surgery for stress urinary incontinence – Patient decision aid, available at: <https://www.nice.org.uk/guidance/ng123/resources/surgery-for-stress-urinary-incontinence-patient-decision-aid-pdf-6725286110>

⁴⁵⁴ U. Ulmsten *et al.*, An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. *International urogynecology journal and pelvic floor dysfunction* **7**, 81-85; discussion 85-86 (1996). <https://doi.org/10.1007/bf01902378>

process Ethicon agreed to pay Professor Ulmsten \$400,000 if the early results that he had achieved with the TVT could be replicated by other surgeons.⁴⁵⁵

- 5.70 Professor Ulmsten's hospital teamed up with five other hospitals and each one carried out around 20 procedures. None of the trial centres received payments from Ethicon. However, Professor Ulmsten was the lead author on the resulting paper.⁴⁵⁶ We understand, on the basis of Ethicon's evidence, that he stood to gain financially from demonstrating that the TVT was as efficacious in other surgeons' hands. The results from the multi-centre trial did demonstrate the same high cure rate and low complication rate, but the paper ends with a note of caution. *'...we must bear in mind that long-term results are necessary before the ultimate pace of a new surgical method can be established. Unfortunately, few surgical methods for the cure of stress incontinence have been exposed to prospective long-term follow up studies. Until such an evaluation has been done the IVS plasty [TVT] can only be characterised as a promising new technique that should be evaluated further in a larger series of prospective studies over a longer period.'*
- 5.71 Despite the recognised limitations of the available evidence the use of mesh for SUI increased substantially, see graph 5.1. This was, in part, due to the actions of SERNIP.⁴⁵⁷ In 1993 the Department of Health was advised to set up *'a committee on safety and efficacy of procedures to review and register novel surgical procedures'* with statutory powers similar to the Committee on Safety of Medicines.⁴⁵⁸ They did not, instead they opted for a voluntary organisation, the Safety and Efficacy Register for New Interventional Procedures (SERNIP), hosted by the Standing Committee of Medical Royal Colleges.⁴⁵⁹ SERNIP made recommendations, but had no enforcement powers and was widely regarded as underfunded and not independent.
- 5.72 In October 1999 SERNIP classified Tension-Free Urethropexy (TFU) also known as TVT, as a Category C product, which meant it should be used in research only. However, three months later, after a challenge to the C rating from the product's manufacturer Ethicon, SERNIP reclassified TVT as Category A, safe to use, and did not make any recommendations on further data collection. The reclassification was based on observational data from conference abstracts, not on peer-reviewed published papers. Had SERNIP been independent, properly constituted and funded,

⁴⁵⁵ Ethicon written evidence to the IMMDS Review.

⁴⁵⁶ U. Ulmsten *et al.*, A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence. *International urogynecology journal and pelvic floor dysfunction* 9, 210-213 (1998). <https://doi.org/10.1007/bf01901606>

⁴⁵⁷ The Safety and Efficacy of New Interventional Procedures.

⁴⁵⁸ Advisory Council on Science and Technology. A report on medical research and health. London: Office of Science and Technology, HMSO 1993;28

⁴⁵⁹ Now known as the Academy of Medical Royal Colleges <https://www.aomrc.org.uk/>

- as in the recommendation made to the Department of Health, we believe that this reclassification may not have occurred.
- 5.73 NICE did not conduct a further assessment or review of the January 2000 reclassification when it replaced SERNIP in April 2000.
- 5.74 In the early 2000s various expert opinions consistently stated that the evidence base for SUI surgery was small, for example Cochrane 2001,⁴⁶⁰ NICE 2003,⁴⁶¹ Cody et al 2003.⁴⁶² A letter to its members from the British Association of Urological Surgeons (BAUS) in February 2004 recognised the lack of evidence and went on to say, *‘The European CE mark constitutes no more than recognition that the product is “fit for purpose” and it is possible for products to become registered with no clinical data at all...’* It continued that there was little prospect of changing the EU-wide regulation of devices and that BAUS had no statutory authority to regulate clinical practice. BAUS and BSUG jointly drew up ‘Good Practice Guidelines for surgeons’ which encouraged reporting surgical outcomes to their respective audit/database.⁴⁶³
- 5.75 Initially professional societies and individual clinicians had been cautious about the TVT. However, this changed. In his oral evidence Mr Mark Slack describes pressure from colleagues, industry and patients to adopt the TVT *‘I almost felt like a pariah in the late ‘90s and early 2000s for not doing a TVT. I was made to feel like I was doing my patients a disservice.’*⁴⁶⁴
- 5.76 Research conducted by the United Kingdom and Ireland Tension-free Vaginal Tape Trial Group, headed by Paul Hilton, was pivotal in encouraging the use of TVT. *‘Ultimately I waited until the Hilton paper on the prospective randomised controlled trial comparing colposuspension and TVT which showed equivalence, effectively.’*⁴⁶⁵

⁴⁶⁰ C. C. B. Bezerra, H. Bruschini, D. J. Cody, J. D. Cody, Suburethral sling operations for urinary incontinence in women. *Cochrane Database of Systematic Reviews*, (2001). <https://doi.org/10.1002%2F14651858.CD001754>

⁴⁶¹ NICE, 2003, Final Appraisal Determination – Tension-free vaginal tape (Gynecare TVT) for stress incontinence, available at: <https://www.nice.org.uk/guidance/ta56/documents/final-appraisal-determination-tension-free-vaginal-tape-gynecare-tvt-for-stress-incontinence2>

⁴⁶² J. Cody et al., Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. *Health technology assessment (Winchester, England)* **7**, iii, 1-189 (2003). <https://doi.org/10.3310/hta7210>

⁴⁶³ See Letter to BAUS members from Colin Lucas dated 24 February 2004 and attached Code of Conduct, appended to the BAUS Written Evidence.

⁴⁶⁴ OH Mark Slack, 23 January 2019.

⁴⁶⁵ K. L. Ward, P. Hilton, UK, T. V. T. G. Ireland, A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. *American journal of obstetrics and gynecology* **190**, 324-331 (2004). <https://doi.org/10.1016/j.ajog.2003.07.029>

The group's first paper, Ward and Hilton 2002,⁴⁶⁶ was a multi-centre prospective randomised controlled trial of TVT versus colposuspension.

- 5.77 This was a key paper in influencing the perceptions of surgeons about the TVT. According to Cody et al 2003⁴⁶⁷ there was a potential bias toward better outcomes with a TVT due to the patients rather than the operation itself. They proposed that the patients in the colposuspension group were generally more severely affected, predisposing them to poorer outcomes, this was because patients with less severe SUI dropped out of the colposuspension arm.
- 5.78 Further publications from the TVT Trial group followed.⁴⁶⁸ Concerns have been raised about support provided by manufacturers to clinicians for evaluating medical devices. Ethicon provided a grant to support Karen Ward's work, which also provided materials and additional support to collaborating centres. Ethicon also funded Paul Hilton and Karen Ward's attendance at conferences where this, and other related work, was presented. Unless all research is to be state-funded it is difficult to see where sufficient funding would come from. However, strong governance arrangements and transparency are needed to ensure public confidence,⁴⁶⁹ as we discuss in Chapter 2, paragraph 2.67.

The Pause

- 5.79 When the pause was put in place it was not based on new data.⁴⁷⁰ The pause was based on listening to existing evidence from affected women; evidence which had been available to the healthcare system for years. The IMMDS Review was formed

⁴⁶⁶ K. Ward, P. Hilton, Prospective multicentre randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. *BMJ : British Medical Journal* **325**, 67-67 (2002). <https://doi.org/10.1136/bmj.325.7355.67>

⁴⁶⁷ J. Cody *et al.*, Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. *Health technology assessment (Winchester, England)* **7**, iii, 1-189 (2003). <https://doi.org/10.3310/hta7210>

⁴⁶⁸ K. L. Ward, P. Hilton, UK, T. V. T. G. Ireland, A prospective multicenter randomized trial of tension-free vaginal tape and colposuspension for primary urodynamic stress incontinence: two-year follow-up. *American journal of obstetrics and gynecology* **190**, 324-331 (2004); Ward KL, Hilton P. Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. *BJOG* 2008;115:226-3310.1111/j.1471-0528.2007.01548.x. <https://doi.org/10.1016/j.ajog.2003.07.029>

⁴⁶⁹ J. Gornall, Vaginal mesh implants: putting the relations between UK doctors and industry in plain sight. *BMJ (Clinical research ed.)* **363**, (2018). <https://doi.org/10.1136/bmj.k4164>

⁴⁷⁰ Letter from Prof Stephen Powis and Dr Kathy McLean at NHSI/E to Acute Trust CEOs and Medical Directors, 9 July 2018, VAGINAL MESH: HIGH VIGILANCE RESTRICTION PERIOD at https://i.emlfiles4.com/cmpdoc/9/7/2/8/1/1/files/47633_mesh-letter-to-acute-ceos-and-mds.pdf; MHRA news update 17 July 2018 available at <https://www.gov.uk/government/news/pause-on-the-use-of-vaginally-inserted-surgical-mesh-for-stress-urinary-incontinence>; BSUG statement on the vaginal mesh high vigilance restriction period, available at: <https://bsug.org.uk/news-details/vaginal-mesh-high-vigilance-restriction-period/76/0/0>

to address the concerns raised by women, but surely others could and should have listened and taken action before.

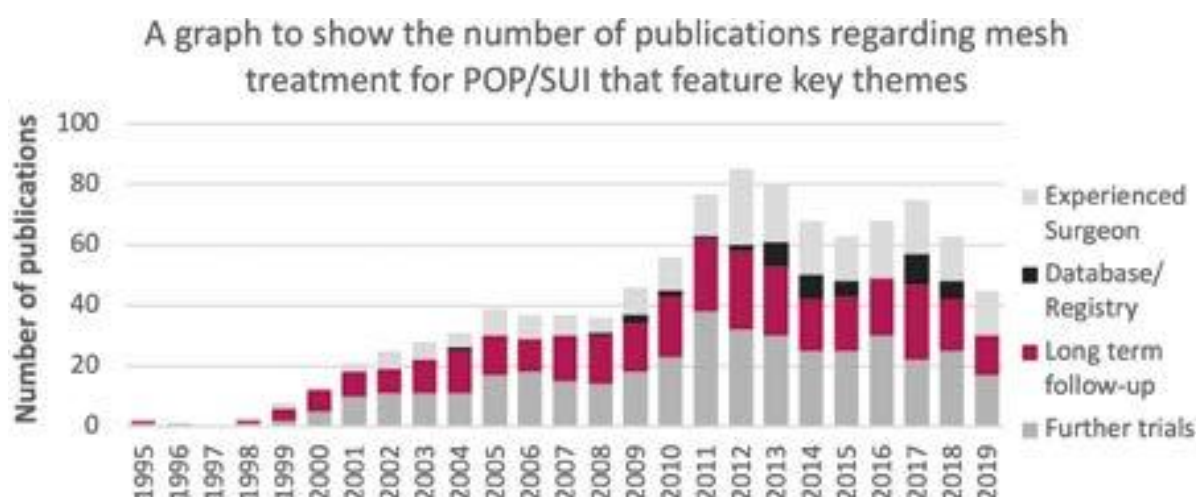
5.80 The conditions that would need to be satisfied before a lifting of the pause could be considered were:

- i. Surgeons should only undertake operations for SUI if they are appropriately trained, and only if they undertake operations regularly;
- ii. They report every operation to a national database;
- iii. A register of operations is maintained to ensure every procedure is notified and the woman identified who has undergone the surgery;
- iv. Reporting of complications via MHRA is linked to the register;
- v. Identification and accreditation of specialist centres for SUI mesh procedures, for removal procedures and other aspects of care for those adversely affected by surgical mesh; and
- vi. NICE guidelines on the use of mesh for SUI are published.⁴⁷¹

5.81 The conditions set out in the pause are not new. As long ago as 2003, NICE guidance on TVT for SUI recommended only experienced surgeons should operate and an audit of numbers of procedures, outcome measures and adverse events should be kept. These themes are also reflected in the published literature on pelvic mesh, see graph 5.2. None of this happened consistently. There were no checks on implementation of the guidance nor enforcement and no consequences for not following it. Had it been implemented, it is likely that many hundreds, perhaps thousands, of women would have been spared mesh complications.⁴⁷²

⁴⁷¹ NICE published guidance NG123 in April 2019 <https://www.nice.org.uk/guidance/ng123>

⁴⁷² NICE do not have enforcement powers for their guidance, so could not have done so.



Graph 5.2 Publications on mesh for POP and SUI that feature key themes 1995-2019

Establishing a mesh database

- 5.82 In future, the conditions set out in the recommendations for the lifting of the pause should remove any ambiguity over who has had mesh surgery. To lift the pause safely the healthcare system has to maintain a database of every mesh procedure undertaken, which can identify every woman who has undergone the surgery and will be linked to MHRA's adverse event reports and to registers constructed to look at long-term outcomes. Surgeons will be required to report all mesh procedures to a national database.
- 5.83 The three professional societies, the British Association of Urological Surgeons (BAUS), the British Society of Urogynaecology (BSUG) and the Pelvic Floor Society (PFS), set up voluntary databases and audits⁴⁷³ because of inertia and inactivity in the healthcare system. As BSUG and PFS said to us '*We were anxious that nobody else was going to*' and '*Well, no one else is doing it*'.⁴⁷⁴ While we applaud any effort to fix this knowledge gap, we are conscious of the limitations of these databases. Their only inputs were from society members, so reporting was done by a limited number of surgeons with a particular interest and expertise. Only the BSUG database has a dataset that is sufficiently mature. There are limited PROMs recorded on the BSUG and BAUS databases and none on the PFS database. Data collection devised by surgeons will tend to focus on surgical outcomes.

⁴⁷³ For background on the databases see HQIP's *Interim Surgical Mesh Database Feasibility Report* (July 2019) available at <https://www.hqip.org.uk/resource/interim-surgical-mesh-database-feasibility-report/#.XilrLvZ2s2w>

⁴⁷⁴ OH BSUG/PFS, 16th April 2019.

- 5.84 When in February 2018 the Secretary of State announced our Review, he also announced that the DHSC would be investing £1.1m ‘to develop a comprehensive database for vaginal mesh to improve clinical practice and identify issues’. The DHSC commissioned from the Healthcare Quality Improvement Partnership (HQIP) a feasibility report on an interim database.⁴⁷⁵ The Healthcare Quality Improvement Partnership’s July 2019 report⁴⁷⁶ proposed two options. First, use the three society databases (BAUS, BSUG and PFS) to form an interim solution. Second, create a new database.
- 5.85 In November 2019 we recommended to the Secretary of State that he issue a Ministerial Direction requiring that a bespoke prospective database for mesh procedures be established and administered by NHS Digital. The Secretary of State agreed to do so immediately, and the Direction was made. We discuss this further in Chapter 2, Theme 10.

Audit and follow up to establish complication rates

- 5.86 If possible, this prospective database should be combined with a selective retrospective audit of a defined cohort of women who have undergone mesh procedures some years ago, in order to establish the rates of complications in the long term. A retrospective follow-up of all women who underwent mesh surgery in one year (2010 has been suggested), or a representative sample from a range of Trusts could be attempted.
- 5.87 We have held initial discussions with NHS Digital on the feasibility of **an audit of the patients who had mesh implantation in 2010**. We recognise that given the historic nature of this exercise, the information available may be incomplete. Nevertheless, we consider it important that every effort is made to understand long-term complication rates.

⁴⁷⁵ HQIP *Interim Surgical Mesh Database Feasibility Report* (July 2019) available at <https://www.hqip.org.uk/resource/interim-surgical-mesh-database-feasibility-report/#.XilrLvZ2s2w>

⁴⁷⁶ *ibid.*

Surgical skills gap – non-mesh surgery for SUI

'2019 NICE Guidelines suggests that TVT/TOT Mesh should only be used as a last resort, but every gynaecologist in the UK is deskilled in performing alternative procedures, so how can TVT/TOT Mesh be used as a last resort?'

Email from Susan Morgan and Vasanta Suddock, Action for Mesh injured patients

- 5.88 The first NICE Health Technology Assessment (HTA) in 2003 states that an experienced surgeon can do three TVTs per day compared to two colposuspensions, and that surgical training is necessary. It also states that expertise is needed in selecting appropriate patients to operate on. Unfortunately, in the use of mesh in SUI neither of these conditions seems to have been met in all cases.
- 5.89 The pause forced surgeons to take stock. SUI mesh underwent a rapid rise in uptake where it became the first-line option. This was driven by a lack of recognition of complications, exacerbated by the long latency of some complications, and reviews⁴⁷⁷ stating that slings were usually preferable to colposuspension. This caused a skills gap; there is a generation of surgeons who have not done non-mesh procedures and need training to perform them. This was acknowledged by Ms Swati Jha of BSUG⁴⁷⁸ *'One of the things that we recognised when the pause came into place is how well-equipped we were, or how poorly equipped we were, to deal with or offer a service to women with incontinence when the mesh was taken away as an option. That made us stop, pause and think about how we were going to address that.'*
- 5.90 Surgeons should not carry on with operations that have been superseded just to 'keep their hand in'. Within clinical networks some operations that are less commonly carried out should continue to be undertaken, where appropriate, by specialist teams, this will ensure that necessary skills are not lost.

Mesh removals

- 5.91 These implants were meant to be permanent; removal surgery is specialist and novel. The removal of transobturator tape is technical and complex surgery and

⁴⁷⁷ N. M. Dean, G. Ellis, P. D. Wilson, G. P. Herbison, Laparoscopic colposuspension for urinary incontinence in women. *The Cochrane database of systematic reviews*, Cd002239 (2006, updated in 2009). <https://doi.org/10.1002/14651858.CD002239.pub2>

⁴⁷⁸ OH BAUS, BSUG, PFS, 7 February 2019.

there are very few surgeons in the UK capable of undertaking this. We have heard from several women who have travelled overseas to have their mesh removed, because they do not feel that UK surgeons have appropriate expertise. In some cases a partial removal had previously been done in the UK. These decisions are not taken lightly and it is almost always at a substantial cost, both physical and financial, borne by the woman and her family. This seems particularly unfair when the complications arise from an NHS operation.

- 5.92 The NHS needs to provide a first-class removal service for women, free of charge, in the UK. Expert consensus is needed in two respects: on whether it should be full or partial removal and what are the best techniques to use. The Royal Colleges, professional associations and specialist clinicians here in the UK urgently need to collaborate with each other and international colleagues to share outcome data and to reach a clinical consensus on mesh removals. Surgeons need to be clear with women about the nature of the procedure they are able to carry out, the technique they intend to use, and possible risks or complications.
- 5.93 A pressing issue for mesh removal is the lack of expert consensus on what type of removal is more appropriate. For example, NICE recommend both partial removal and full removal, but we have heard from some surgeons that full removal should be the preferred option and from others that partial removal or two stage removal is most appropriate for some women. We recognise that NICE guidance can only reflect the opinions of the experts they consult, as removals are a new and emerging area. The April 2019 NICE guidance [NG123]⁴⁷⁹ ‘Urinary incontinence and pelvic organ prolapse in women: management’ provides information on partial and full removals in the event of mesh complications. No preference is expressed either for full or for partial removals.
- 5.94 Women have told us they were treated as ‘guinea pigs’ at implantation and are now being treated as ‘guinea pigs’ again over mesh removal. Collective expert opinion is urgently needed so that a consensus can be reached; firstly, on the partial versus full removal debate and secondly, on the best surgical technique to use.
- 5.95 We understand the International Continence Society intends to draw up a position statement on this issue. Without an evidence base to indicate whether full or partial removal has the better long-term clinical outcomes, and without a clinical consensus on merits of different procedures or the techniques involved, it is impossible for mesh-affected women to know what is best. Urgent research and international collaboration are needed to resolve this. **A consensus needs to be reached on whether it is better to carry out full or partial removals. This is a**

⁴⁷⁹ NICE Guidance [NG123] ‘Urinary incontinence and pelvic organ prolapse in women: management’ (April 2019) available at <https://www.nice.org.uk/guidance/ng123>

clinical matter, and it must be done collaboratively. This consensus should be validated by carrying out follow up on those who have removals at the specialist centres. We strongly recommend that NICE actively monitor the situation and update their guidance promptly once a consensus has been reached.

- 5.96 We have an additional concern in respect of mesh removal. We have had reports from some women about confusing terminology used by clinicians when discussing removals. Women have been offered a ‘full vaginal removal’ and understood that this operation would remove all their mesh. A ‘full vaginal removal’ is the removal of the vaginal portion of the mesh, leaving the rest of the mesh in situ.
- 5.97 There is a lack of clarity in the April 2019 NICE Guidance [NG123], at point 1.11.7 it states *‘Discuss with women who have vaginal complications after mesh sling surgery for stress urinary incontinence that: complete removal of the vaginal portion of mesh sling is associated with a greater risk of recurrence of stress urinary incontinence than partial removal.’* This seems to imply that a removal of a part of a mesh is not the same as a partial mesh removal.
- 5.98 As with insertions the terminology used around removals is variable and could be confusing at best, misleading at worst. Far greater clarity and consistency is needed on terminology; defining of terms must involve both patients and clinicians. In November 2019 the Scottish Government announced a review into this issue.⁴⁸⁰

Our statement on our concerns over partial mesh removals

- 5.99 We were so concerned by this issue that we raised it at the highest levels at DHSC and with NHS England. On 13 December 2019 we put out a statement⁴⁸¹ recommending the following requirements be put in place as soon as possible in all cases where mesh removal is carried out:
- All mesh removal procedures must be conducted under a high-vigilance regime;
 - All decisions about a woman’s suitability for a mesh removal procedure and the nature of that procedure must be taken by an appropriately trained and expert multi-disciplinary team;

⁴⁸⁰ Question S5W-25668: Neil Findlay, Lothian, Scottish Labour, Date Lodged: 11/10/2019, available at: <https://www.parliament.scot/parliamentarybusiness/28877.aspx?SearchType=Advance&ReferenceNumbers=S5W-25668&ResultsPerPage=10>

⁴⁸¹ IMMDSR statement, ‘Our concern over partial mesh removals’, 13th December 2019, available at: <https://www.immdsreview.org.uk/news.html>

- The operating surgeon must possess the necessary skills and competencies to carry out the procedure;
- The patient must be fully informed with the support of a patient decision aid;
- Consent must be recorded and be based on clear, unambiguous language;
- All explanted mesh should be measured, and images taken of it;
- All removal procedures should be appropriately coded and entered onto a database;
- Outcomes must be monitored and recorded over an appropriate timeframe, including patient-reported outcomes.

Specialist mesh centres

‘...the patient has to feel like they’re able to heal. The patient has to be looked after, given the medical services and allowed to walk out of this mesh world and not have their life defined by mesh. Some women will have their scars, their emotional scars and their health scars, for their lifetime.’⁴⁸²

Mary McLaughlin, Mesh Ireland

5.100 We have met mesh-affected women with serious healthcare needs who have lost faith in, and feel abandoned by, the medical professional and the wider healthcare system. This urgently needs resolving. Our recommendations, which are intended to begin the process of restoring trust in the system, include specialist centres for treating mesh complications (see **Chapter 1, Recommendation 5**). We envisage these as taking a multidisciplinary, holistic approach to meet mesh-injured women’s needs. We have been in discussion with NHS England to ensure that the service specification for these centres includes core health services, such as expert mesh removal surgery, appropriate imaging, pain clinics and pelvic physiotherapy, and also other ancillary services, including psycho-sexual counselling. In addition, we would like to see help signposting the benefits systems co-located within the centres. We hope that these specialist centres will provide mesh-injured women with first-rate care and will reassure them that their needs are being taken seriously. A hub and spoke model with an emphasis on MDT working is envisaged;

⁴⁸² OH Mesh Ireland, 20 May 2019.

these are described in NHSE's commissioning specification. Specialist Centres treat all the complex patients, so they have oversight of mesh injuries that other hospitals cannot have. As such, it is our view that specialist centres must carry out research. These centres will also enable us to find out far more about what happens when mesh surgery goes wrong and why it goes wrong. **These specialist removal centres can also serve as the hub for clinical networks which should provide support for teams undertaking surgery for SUI and POP.** We have discussed the possibility of transitional arrangements whereby some centres offer simpler removals initially, and progress to offering more difficult removals only when they have developed their skills base. We hope these centres will be the first step towards rebuilding their trust in doctors.

- 5.101 An issue that has been commonly raised is that the surgeons carrying out mesh removal may also implant mesh. While the pause remains in place UK surgeons will only implant mesh in exceptional circumstances. However, we recognise that these concerns are about intentions as much as practice. We have had discussions with surgeons (national and international) who both remove and insert synthetic mesh, and with their patients who have high levels of confidence in them. We were reassured that trust could be built in these circumstances, founded on open honest dialogue with an emphasis on listening.
- 5.102 We discussed credentialing with Professor Derek Alderson of the RCS in the context of mesh surgeries. The RCS considered that it would be difficult to credential a broad area of practice, or even a sub-specialty, as these comprise a number of highly-specialised and varied surgeries. Instead, they suggested **credentialing a small number of centres and surgeons for particular complex surgeries.** The quality could then be monitored through annual appraisal.⁴⁸³ These standards could also be taken into account as part of CQC inspections, as is the case for cosmetic surgeries. In our view, the work carried out in credentialing so far represents a positive step in providing assurance to patients and the public.
- 5.103 We were told that the final service specification will include psychosexual counselling, pelvic pain clinics and physiotherapy. In their oral evidence the British Pain Society (BPS) reported a chronic underfunding of pelvic pain services.⁴⁸⁴ These services are essential to mesh-injured women and must be made available. The hub and spoke model for the specialist mesh centres should be used to spread expertise. But specialist centres are in addition to, and not a substitute for, these services being provided as standard by Trusts.

⁴⁸³ OH, Royal College of Surgeons, 7th February 2019.

⁴⁸⁴ OH, British Pain Society, 7th February 2019.

- 5.104 There is also a need for wider support for other services such as benefits eligibility and payment issues and social care. These services should either be signposting from, or co-located within, the specialist centres. We have been told that when damage is attributed to mesh the benefits and social care services offered are not adequate. Many women have said that PIP assessments are fundamentally unsuitable, they describe a lack of awareness by assessors of mesh complications and the impact they have on lives. *'Benefit assessors are forever patient shaming. We've had this experience, I went myself. This has really got to stop, and somebody needs to stand up and help us in this because our injuries are so taboo and it's very difficult. My assessor was meant to have been a male. Luckily he was away that day and so I was assessed by a female and she was absolutely horrible.'* Jemima Williams Welsh Mesh Survivors⁴⁸⁵ The way in which assessments are repeated even when there has been no improvement in a woman's condition has been raised as a source of stress and concern. We say more about the Department for Work and Pensions (DWP) assessment process in Annex I.
- 5.105 Whilst the specialist mesh centres we have recommended are being implemented the support for women affected by mesh remains unsatisfactory. A **remote counselling service along the lines we set up during this Review should continue to exist.**
- 5.106 We have discussed with NHS England's Specialised Commissioning team⁴⁸⁶ our concerns that the demand for specialist mesh removal centres is being estimated using HES data on the numbers of mesh removal operations which are currently undertaken. We have concerns that HES data underestimates the demand for mesh removal surgery. Women may not be coming forward for removal because they have lost faith in the medical profession. Women who have had removal surgery privately, either in the UK or abroad, are not included in HES data. The assumptions used to calculate uptake may under-represent the true complication rates.
- 5.107 The specialist mesh centres are being commissioned as part of the women's health portfolio. As part of this Review we have considered the use of mesh in rectopexies, which can affect both men and women. We have heard in evidence from the PFS that the mesh complication rates for rectopexy are far lower than those for SUI and POP mesh, around 1% based on their database.⁴⁸⁷ However, rectopexy surgery should only be undertaken by appropriately-trained surgeons. We discussed this issue with NHS England, and as a result of those discussions they are considering the issues of rectopexy and co-location of rectopexy with specialist mesh services.

⁴⁸⁵ OH Welsh Mesh Survivors, 21 November 2019.

⁴⁸⁶ We have had regular meetings with them to ensure we are kept up to date of developments.

⁴⁸⁷ OH BAUS, BSUG, PFS, 7 February 2019.

As with other mesh procedures there is a need for more data on complication rates following rectopexies. The devices database and the pelvic floor registry, detailed under the Direction the Secretary of State has issued, should provide clinical outcomes data on mesh and comparator non-mesh operations.

EU Regulation of Devices

- 5.108 The system for regulating devices is relatively immature compared to medicines regulation, see Annex H History of Regulation and Chapter 2 Theme 11 – Regulation going forward. It has not had the same length of time to develop and to become fit for purpose. In 1967 there were discussions about incorporating medical devices in the Medicines Act 1968,⁴⁸⁸ but device regulation was not included. There was then a wait of almost three decades until the mandatory regulation from mid-June 1998. SUI slings were first marketed in 1996, so for the first two years they were available there was no mandatory EU medical device regulation.
- 5.109 EU medical devices are not licensed,⁴⁸⁹ instead they are certified to show they meet legal requirements on safety and performance. Once it has met the requirements set out in legislation a device can be CE marked by the manufacturer, this CE mark allows it to be sold throughout the EU without any further checks.⁴⁹⁰ Devices can be certified either because they have undergone premarket testing to establish safety and performance or because they can demonstrate that they are equivalent to a device that is already on the market.⁴⁹¹ The vast majority of pelvic mesh products were certified based on equivalence.
- 5.110 There are two types of adverse event report for devices. Spontaneous reporting which we cover in **Chapter 1, Recommendation 6** and Chapter 2, Theme 11. Devices also have mandatory reporting from manufacturers. Women describe adverse outcomes such as pain or sexual difficulties. However, these types of outcomes are not necessarily reflected in the adverse events reported by manufacturers. As John Wilkinson, the former Head of Devices at the MHRA, told us in oral evidence *‘So the obligations on manufacturers are to report incidents which involve above a certain threshold of seriousness, but effectively that has to be linked to the performance of the product per se. There is some grey in that interpretation, I would say.’* If a manufacturer does not interpret the adverse event suffered to be

⁴⁸⁸ MH 168/15 National Archives.

⁴⁸⁹ This is similar to the US, where devices are approved rather than licenced.

⁴⁹⁰ Annex H on History of Regulation (Part 2).

⁴⁹¹ In the US similar process is used to demonstrate equivalence, the 510k process.

sufficiently serious or to be linked to the performance of the devices there is no obligation to report it to the MHRA.

- 5.111 Article 20 of the Medical Devices Directive (MDD) places restrictions on what the MHRA can disclose about conversations with device manufactures. In our oral hearing John Wilkinson of the MHRA stated *‘I think there’s some merit in not being completely transparent about every interchange that happens while you’re doing an investigation, otherwise that investigation could be compromised. But ultimately, those provisions go too far and certainly the provisions around publication of adverse events and the information around those, I think there is no reason why those shouldn’t be in the public domain.’* The MHRA also told us they had not succeeded in changing these provisions at EU level in the new Medical Devices Regulations, so they were introducing a voluntary initiative to encourage manufacturers to increase transparency and openness around adverse events.
- 5.112 We have recommended the creation of a searchable adverse event database for the UK for both devices and medicines, which contains all device adverse events reports; see **Chapter 1, Recommendation 6** and Chapter 2, Theme 11.
- 5.113 ‘Equivalence’ is not defined in the MDD, which seems to us to be a serious omission. The pelvic mesh story contains examples of CE marked devices claiming equivalence to a device made from a totally different material,⁴⁹² or claiming equivalence to a device that has the same function, but is implanted in a different way.⁴⁹³ This interpretation of equivalence has enabled ‘product creep’ to occur - devices several generations later may bear scant resemblance to the original. We recognise that medical devices evolve, and design improvements are made iteratively. We welcome efforts to rebalance ‘equivalence’ in the new EU Regulations. The MDR will not automatically become UK law, but we understand the UK will adopt equally stringent provisions.⁴⁹⁴
- 5.114 We were disturbed to find that under the MDD a manufacturer could certify their device for sale in the EU on the basis that it was equivalent to a device that had never been CE marked or used or sold in the EU. For example, Ethicon’s market-leading TVT certification included equivalence to Boston Scientific’s ProteGen sling, despite the fact that the ProteGen had never been CE marked and sold in the EU. We are pleased that the new Regulations state that equivalence can only be claimed to a device that has already been marketed in the EU.

⁴⁹² For example, the ProteGen sling was made of polyester, but the TVT which claimed equivalence to it is made of polypropylene.

⁴⁹³ The TVT-O is implanted very differently to the TVT, but was certified as an equivalence product.

⁴⁹⁴ IMMDS Meeting with MHRA on 1 May 2020.

- 5.115 If a predicate device is withdrawn for safety reasons, as the ProteGen sling was in 1999, there is no automatic reassessment of daughter devices. The lack of any centralised information on devices puts the onus on individual manufacturers and notified bodies to monitor product withdrawals and safety communications and to check if they are relevant to any of their devices. The new register of devices that we are proposing will help to resolve this situation in the future (see **Chapter 1, Recommendation 6**).

National regulators

- 5.116 In England and Wales we have a unique synergy between the MHRA which regulates the marketing of devices and NICE who recommend how products should be used. Most other product regulators, such as the FDA in the USA and the Therapeutic Goods Administration (TGA) in Australia, do not have a NICE equivalent providing guidance on what is appropriate device usage. The MHRA has sometimes been perceived as lagging behind other international regulators (see paragraphs 5.6 – 5.7 and Annex G Pelvic Mesh Supporting Information) and tending to rely on advice from NICE. This is a reflection on the distinctive arrangement here. There is clear benefit to having the way in which a product is used separated from an agency that regulates the sales of that product. This is particularly so for medicines where that part of the MHRA is funded by levies from the pharmaceutical industry. However, for this arrangement to function, the recommendations from NICE have to be both evidence-based and implemented. In the case of pelvic mesh this has not happened; NICE had only partial evidence available to consider and various of their recommendations, such as a database and conservative treatments prior to surgery, were not actioned.
- 5.117 All assessments by NICE, the MHRA and others concluded that the ‘benefit outweighs the risk’. Although it needs to be recognised that the data on which they based this opinion did not include outcomes on adverse effects, such as pain and sexual dysfunction.
- 5.118 In the future, as more evidence on patient-specific risk factors becomes available, we would expect NICE guidance to become more tailored. For example, if a medical device, such as mesh, presents a higher risk of complications in women with autoimmune disorders we would expect NICE guidance to reflect this.

Litigation

- 5.119 We have heard about considerable financial hardship caused by mesh, sometimes caused by inability to work and sometimes by the cost of additional private treatment. Many women have raised with us the difficulty in obtaining financial compensation from the current litigation system. Legal action can be brought on the basis of negligence against a healthcare professional (medical negligence) or on the basis of Product Liability (a manufacturer may be liable for damage under the Consumer Protection Act 1987 (CPA) or on the basis of negligence).
- 5.120 The basic limitation period for claims under the CPA is three years from the date of damage or injury. However, as any damage may not be immediately obvious an alternative period of three years from the date when the patient knew – or could reasonably have known – of the claim is available. A product may remain in circulation for many years, but a claim cannot be made more than 10 years after the product was put into circulation. This has caused considerable difficulty with mesh as there are often long latency complications that may not become apparent until many years after the mesh has been implanted.
- 5.121 Some women have succeeded in establishing that their surgeon has been negligent, either in the way the operation was performed or by not providing enough information so the women could give informed consent. We recognise that there are difficulties in establishing negligence and we wish to see a new redress system as described in **Chapter 1, Recommendation 3**. We recognise that many women have suffered avoidable harm and we are recommending an *ex gratia* scheme to provide need-based payments to help those affected by mesh injuries. In our view both the government and mesh manufacturers have an ethical obligation to contribute to this fund, **Chapter 1, Recommendation 4**.

Finally

- 5.122 We have identified relevant issues and actions, set out in our Recommendations 3, 5, 6 and 7 of Chapter 1, and in Actions for Improvement detailed in the text above. In addition, we propose the following:
- 5.123 Prevention is better than a cure. We agree with the suggestion from Olive McIlroy and Elaine Holmes of Scottish Mesh Survivors *‘We would also call for the introduction of pelvic floor exercises to be routinely offered to all pregnant women and female high school pupils and greater importance given to prevention.’* Open frank discussions on pelvic floor disorders and incontinence normalises these issues and reduces stigma. Using the correct terminology equips women with the language they need. **Pelvic floor education should be encouraged,**

where appropriate, in schools and certainly in antenatal classes. In addition, we recommend that the NHS adopts the French model for universal post-natal pelvic floor rehabilitation.

- 5.124 Dismissive, defensive attitudes by surgeons are a cultural issue that needs to be addressed by the medical profession, its professional bodies and regulators.**

- The current position:
 - Mesh for the treatment of Stress Urinary Incontinence is paused until the conditions recommended for the lifting of the pause are met;^a
 - Mesh cannot be used transvaginally for Pelvic Organ Prolapse unless the operation is part of a research trial (NICE Interventional procedures guidance IPG599)^b;
 - Other abdominal pelvic organ prolapse mesh procedures, including rectopexies for rectal prolapse, can only be carried out under 'high-vigilance' regimes.^a
- In our opinion the current data does not reflect true complication rates. Twenty years after mesh started to be used in the pelvis we still do not know its long-term risk profile. The same is true for mesh removals. Women were not warned about the risks they faced (known and unknown) leading to avoidable harm for a significant number.
- An apology is due, and support is required for those who have suffered avoidable harm.
- We have not recommended a complete ban on the use of mesh in the treatment of urinary incontinence or repair of pelvic organ prolapse. Regulators should review this in the light of new and more accurate long-term, patient-focussed outcome data.
- We have discussed with NHS Digital an audit and follow-up of all pelvic mesh surgery carried out in 2010. If feasible, this should provide more accurate complication data.
- One of the conditions for lifting the pause is the identification and accreditation of specialist mesh complication centres. The process of commissioning these has started. However, there is still no consensus on how to treat those complications and what type of removals/procedures are best.
- If the conditions for lifting the pause are met and the pause is lifted, then mesh implants should only be considered after all the options for conservative and non-mesh surgery have been explored.

^a Letter from Prof Stephen Powis and Dr Kathy McLean to Acute Trust CEOs and Medical Directors, 9 July 2018, VAGINAL MESH: HIGH VIGILANCE RESTRICTION PERIOD, available at https://i.emlfiles4.com/cmpdoc/9/7/2/8/1/1/files/47633_mesh-letter-to-acute-ceos-and-mds.pdf and Letter from Prof Stephen Powis and Dr Kathy McLean to Regional Directors, Trust Medical Directors, and clinicians involved in the care of patients with stress urinary incontinence and pelvic organ prolapse, 29 March 2019, EXTENSION OF PAUSE TO THE USE OF VAGINAL MESH, available at: https://improvement.nhs.uk/documents/5122/MESH_letter_-_Extension_of_pause_on_the_use_of_vaginal_mesh_29_March_2019.pdf

^b NICE Interventional procedures guidance IPG599 available at <https://www.nice.org.uk/guidance/ipg599>

Recommendations and Actions for Improvement	
See Chapter 1, Recommendation 5	5.12-5.13, 5.100
See Chapter 1, Recommendation 7	5.14, 5.50,
Further research is urgently needed so that a clearer view can be reached on the inherent properties and safety of pelvic mesh.	5.33
Medical device manufacturers must research and develop a remedial strategy to address any severe complications caused by their product. This strategy should be set out in the Instructions for Use (IFUs) and guidance. The strategy should be developed collaboratively with appropriate input from others, such as the regulators and the commissioners of any services required to carry out actions.	5.38
See Chapter 1, Recommendation 6	5.50, 5.110, 5.112, 5.115
We recommend that when a device or procedure is introduced a cohort of early recipients undergo enhanced reporting to detect unexpected adverse impacts.	5.52
NICE's most recent guidance states that the TVT-O should not be offered routinely. In the future, we feel the TVT-O should only be used in exceptional circumstances, if at all.	5.55
Professional bodies should lead on ensuring surgeons only operate within their capabilities. They must provide guidance for their members and ensure that surgeons are appropriately trained, and this should be assured through the appraisal process	5.56
A culture must exist where all MDT members feel able to speak up and that their input will be listened to. Trusts must work to create a culture that facilitates effective MDTs.	5.58
Conservative measures must be offered to women before surgery. We have heard that specialist pelvic floor physiotherapy cannot match the current demand. The service commissioner should identify gaps in the workforce and notify specialist clinicians, professional organisations and Royal Colleges. A co-ordinated strategy can then be developed to remedy the gap.	5.59
Clinicians must ensure patients have sufficient understanding of their treatment, including the benefits, the potential risks it presents, and the alternative treatment options, including doing nothing, in order to decide whether they are willing to have that treatment.	5.60

Recommendations and Actions for Improvement	
Clinicians need to establish and agree terminology and definitions related to both mesh insertions and removals.	5.68
An audit to establish complication rates should be attempted using the women who had mesh insertions in 2010.	5.87
A consensus needs to be reached on whether it is better to carry out full or partial removals. This is a clinical matter, and it must be done collaboratively, including consulting international experts. This consensus should be validated by carrying out follow up on those who have removals at the specialist centres. We strongly recommend that NICE actively monitor the situation and update their guidance promptly once a consensus has been reached.	5.95
Consideration should be given to credentialing a small number of centres and surgeons for particular complex pelvic mesh surgeries.	5.102
A remote counselling service along the lines we set up during this Review should continue to exist.	5.105
See Chapter 1, Recommendation 3	5.121
See Chapter 1, Recommendation 4	5.121
Pelvic floor education should be encouraged, where appropriate, in schools and certainly in antenatal classes. In addition, we recommend that the NHS adopts the French model for universal post-natal pelvic floor rehabilitation.	5.123
Dismissive, defensive attitudes by surgeons are a cultural issue that needs to be addressed by the medical profession, its professional bodies and regulators.	5.124

6 Public Inquiries

‘...and fourthly, whether we need an independent system to decide what further action maybe required either in these three cases or in the future. This is because one of the judgements to be made is whether, when there has been widespread harm, there needs to be a fuller or even statutory, public inquiry. Baroness Cumberlege will make recommendations on the right process to make sure that justice is done and to maintain public confidence that such decisions have been taken fairly.’⁴⁹⁵

Rt Hon Jeremy Hunt MP, former Secretary of State for Health and Social Care

- 6.1 The call for a ‘public inquiry’ into an event of major public concern resulting for example from large scale loss of life, serious health and safety issues or failure in regulation has been a common occurrence in recent years. They can be set up to consider the events of a one off incident or multiple incidents occurring over decades. They are nearly always complex and multifaceted, most often established in the context of political controversy accompanied by a considerable amount of publicity, Parliamentary lobbying and pressure group campaigning.
- 6.2 Although differing in their nature, size and subject matter public inquiries will invariably seek to answer the following questions:
 - what happened?
 - what can be learnt to prevent this happening again?
- 6.3 If run with those most affected by the events under consideration at the heart of the process, public inquiries can achieve some therapeutic resolution as tragic stories are told and differing perspectives are listened to. They provide an important stepping stone in trying to restore public confidence in a system that has allegedly failed, and an acknowledgement that ‘something is being done’. Although a public inquiry is not permitted to make findings of criminal or civil liability, it will search for the truth and make findings of fact accordingly. Where appropriate this may include identifying those who are at fault.

⁴⁹⁵ Secretary of State for Health’s statement to the House of Commons, 21st February 2018. <https://hansard.parliament.uk/commons/2018-02-21/debates>

- 6.4 Inquiries, though independent, are usually established by Ministers, funded by Government and accountable to Parliament for their spend. It will be for the Minister to decide, usually on advice, whether an inquiry should be statutory – normally held under the Inquiries Act of 2005 – or non-statutory. Non-statutory inquiries allow for greater flexibility in determining their own processes and procedures but in the absence of statutory powers, they must rely on the voluntary compliance of witnesses and the production of documents and cannot take evidence under oath. In consequence, they tend to be both less legally hidebound in content and less adversarial in tone and style.
- 6.5 Central to the decision to hold a public inquiry (whether statutory or not) must be whether it is in the public interest to do so and at what cost. Public Inquiries are expensive and lengthy, factors that of themselves can dent public confidence in the inquiry process. The National Audit Office (NAO) identified 26 government-funded inquiries between 2005-17, of which 15 were carried out under the Inquiries Act of 2005.⁴⁹⁶ The total cost of all 26 was at least £239 million – of which the largest single component were legal fees averaging 36% of the total - and the average duration was over three years.⁴⁹⁷ Other significant costs included running and other staff costs – costs that vary directly with the length of time an inquiry takes. The longer the duration the more inevitable the risk that their impact will be lost and their findings become less relevant.

The IMMDS Review

- 6.6 Our own Review was set up as an independent, non-statutory inquiry. During the course of our work we have given considerable thought as to whether we should have been set up as a statutory inquiry and whether that would have affected any of our findings and recommendations. Most importantly, would a statutory inquiry have better facilitated the restoration of trust both in the healthcare system and the inquiry process itself. We believe not.
- 6.7 Across all our three interventions there have been calls by Parliamentarians for the Government to commit to a full public inquiry.
- in the case of Primodos and Hormone Pregnancy Tests, the first such call came in 1978 and similar calls have been repeated by Parliamentarians in 2014, 2017, 2018 and 2019, with the emphasis placed on investigating

⁴⁹⁶ NAO 'Investigation into Government- funded Inquiries' May 2018 <https://www.nao.org.uk/wp-content/uploads/2018/05/Investigation-into-government-funded-inquiries.pdf>

⁴⁹⁷ *ibid.* In the Mid – Staffordshire Hospital Inquiry 67% (or £9.1million) of the cost of the Inquiry was due to legal costs.

forensically and transparently all the available evidence and potential regulatory failures;

- in the case of Sodium valproate, the first such call came in 1983 and again in 2013 and 2017 seeking to understand how Epilim and other teratogenic anti convulsants had been allowed to cause so much damage for so long;
- and in the case of pelvic mesh, the first such call came in 2017 seeking a mandatory audit of all women implanted with mesh followed by a full public inquiry to learn the lessons and establish the full facts regarding the risks associated with the use of pelvic mesh implants.

6.8 What the Parliamentarians want, however, is not uniformly what patients and their families want. The patient groups we have worked with consistently throughout this Review have been united in their fervent endeavours to bring their concerns to the public, media and Government's attention. They are rightly seeking answers to their questions, they have brought pressure to bear on the government to investigate what has happened to them and the affected families they support and to ensure lessons will be learned. They are not, however, united in their desire for a statutory public inquiry. And in some cases views have shifted during the course of our work. As one patient group representative told us:

'I found as time has passed and more evidence has come to the fore my views have changed. After watching our oral evidence [to the Review] in which we pursued a public inquiry..... this may not be what families want:

- *a PI [public inquiry] is a leap into the unknown and I feel we would have little power over how the process would be run;*
- *a PI would involve more work for patient groups*
- *a PI would involve emotional pressure on families (revisited and shared private experiences can be a traumatic process)*

*My conclusion is that outcomes are more important than how we get there, and that focusing on what we need now, rather than whose fault it was, would benefit us more.'*⁴⁹⁸

⁴⁹⁸ Susan Cole, Valproate Victims from an email to the Review.

6.9 We have looked long and hard at our processes and what we have been able to achieve within a non-statutory Review framework. Save for one exception, we found:

- we did not need statutory powers to gain access to closed Government files that we were asked to look at by one of the patient groups;
- having statutory powers would not have assisted in addressing questions of legal professional privilege. If it is not possible to resolve an issue of permission arising from legal professional privilege, an inquiry would need to consider how best to proceed. For example, in the absence of any agreement, whether an application to Court should be made. This would inevitably result in delay and additional cost, which a statutory inquiry might be better placed to absorb;⁴⁹⁹
- we did not need statutory powers to make an early recommendation leading to the immediate introduction of a ‘pause’ and the cessation in the use of mesh for the treatment of stress urinary incontinence;
- we did not need statutory powers to recommend a scheme of redress provision.

6.10 The one exception is potentially important. It relates directly to the power to compel witness compliance and document production. Whilst noting that it is possible for documents to come to light by other means, the absence of a sworn affidavit to the contrary meant we could not be sure that all the documentary evidence we sought was in fact provided. We do, however, believe we have sufficient documentary evidence to tell a compelling story of system failure. Without the powers to apply for a witness summons we could not compel witnesses from this jurisdiction or any other (in relation to the manufacturers) to attend an oral hearing. Nonetheless, we were sufficiently dogged to take matters to the Chief Executive’s office where necessary, to ensure continuous engagement at the highest level through written question and answer correspondence, and that evidence is available on our website.

6.11 It is worth noting, too, that statutory powers cease when an inquiry comes to an end and therefore do not confer any statutory requirement to implement the recommendations of an inquiry. Indeed, Governments are under no obligations to do so.⁵⁰⁰ Moreover, as the NAO concluded: *‘There is no organisation across*

⁴⁹⁹ See reference to an issue of legal professional privilege in Appendix 4 paragraph 65.

⁵⁰⁰ *ibid.* The NAO report concluded that in eight out of ten of the inquiries looked at 45% of recommendations were accepted, 33% were accepted ‘in principle’, ‘partially accepted’ or ‘subjected to wider reform’, 7% were explicitly rejected and no clear response was given to the remaining 15%.

*government or Parliament with responsibility for monitoring and tracking whether recommendations have been implemented and ensuring that inquiries have the intended impact.*⁵⁰¹

- 6.12 Ultimately, the decision to hold a public inquiry with the full panoply of statutory powers must be a political one. We do not believe, having considered the evidence before us, that a public inquiry would best serve the interests of those affected by each of the interventions we reviewed. Nor do we believe that we are best placed to define what should be the trigger for such an inquiry in the future, over and above some clearly well-established considerations concerning the scale and impact of harm suffered and the sensitivity of the issues involved. Indeed, we have seen no appetite in favour of a consistent approach to these decisions nor a willingness to ensure any consistent cross Government improvements in the effectiveness and efficiency of inquiries. Rather the opposite. According to the NAO, a number of Cabinet Office and Ministry of Justice commitments given since 2014 to implement such recommendations from two House of Lords' Select Committee reports remain unfulfilled.⁵⁰²
- 6.13 It is our view that both statutory and non-statutory inquiries have a role to play where matters of great public concern come to the fore and where the emphasis needs to be on learning for the future. To restrict inquiries to only the statutory kind would lead to fewer of them because of the expense likely to be incurred and the time it takes to complete them. What matters more is that all independent inquiries and reviews are fit for the purpose they have been set up to investigate, that they have the Panel structure, competencies and skills they need to deliver their Terms of Reference and that they are properly resourced.

⁵⁰¹ *ibid.*

⁵⁰² NAO 'Investigation into Government-funded Inquiries' May 2018 <https://www.nao.org.uk/wp-content/uploads/2018/05/Investigation-into-government-funded-inquiries.pdf>

7 Implementation

- 7.1 Our recommendations are designed to pave the way for a future healthcare system that looks and feels very different. If accepted, in principle, they now need to be implemented with a sense of urgency and real determination to stop future harm and provide care and support for those affected. Acceptance of our findings is the basis for action, not a substitute for it.
- 7.2 We have learned a great deal over the last two years about what needs to be done next. More than that we have a far better, collective understanding of what it means to be affected by Primodos, valproate and pelvic mesh. We have listened to, and collated, the stories of so many patients and families - their suffering, their grief, their pain. Stories that have inspired, informed and influenced us at every stage of our work. With the end of the Review this collective knowledge disappears with us. We cannot keep these stories – the law is quite clear on that. But that doesn't mean that the knowledge and understanding we have acquired, which the system has not, should not now be channelled into the what happens next to implement our recommendations.
- 7.3 The implementation phase should be realistic but ambitious to deliver the help where needed and prevent further harm. **We recommend that the Secretary of State sets up an implementation task force without delay to oversee progress (Chapter 1, Recommendation 9).** Its first task should be to set a timeline for its work and for the delivery of this Review's recommendations.
- 7.4 The task force should be made up of representatives of the various arms of the healthcare system that have a recognisable part to play in delivering patient safety. The Chair of the task force should be someone that is credible with patient groups and has a range of skills that can encourage, support and push implementation forward. The collective knowledge of the Review should also be represented on the task force. This legacy would provide a useful reality check on the implementation process and would ensure continuity of thinking.
- 7.5 Those responsible for implementation need to know their progress will be monitored and they will be held accountable. Supporting the implementation process should be a reference group made up of a range of patient interests going far wider than the groups we have been privileged to work with. It might include for example those charities or others with knowledge of the benefits system and mental health issues. It should receive regular progress reports from the task force

and be able to ask of it such questions as ‘How?’, ‘When ?’ and ‘ Why not?’ It will also ensure that what emerges from the implementation phase is a system that is grounded in the patient experience. The patient groups will themselves have views about how this reference group should be constituted and work.

- 7.6 On behalf of those affected we cannot stand by and let our recommendations gather dust. We expect the Government to take our thoughts on implementations as seriously as they should our Recommendations. If it does we believe we will achieve what is necessary in order to help build a *‘system that listens, hears and acts with speed, compassion and proportionality...’*

8 Summary of Recommendations and Actions for Improvement

Recommendations of the IMMDS Review

Recommendation 1: The Government should immediately issue a fulsome apology on behalf of the healthcare system to the families affected by Primodos, sodium valproate and pelvic mesh.	1.28
Recommendation 2: The appointment of a Patient Safety Commissioner who would be an independent public leader with a statutory responsibility. The Commissioner would champion the value of listening to patients and promoting users' perspectives in seeking improvements to patient safety around the use of medicines and medical devices.	1.29 – 1.32, 2.132
Recommendation 3: A new independent Redress Agency for those harmed by medicines and medical devices should be created based on models operating effectively in other countries. The Redress Agency will administer decisions using a non-adversarial process with determinations based on avoidable harm looking at systemic failings, rather than blaming individuals.	1.33 – 1.37, 2.37, 5.121
Recommendation 4: Separate schemes should be set up for each intervention – HPTs, valproate and pelvic mesh – to meet the cost of providing additional care and support to those who have experienced avoidable harm and are eligible to claim.	1.38 – 1.39, 2.33, 3.137, 4.102 – 4.104, 5.121
Recommendation 5: Networks of specialist centres should be set up to provide comprehensive treatment, care and advice for those affected by implanted mesh; and separately for those adversely affected by medications taken during pregnancy.	1.40, 2.31, 3.136, 4.100 – 4.101, 5.12 – 5.13, 5.100
Recommendation 6: The Medicines and Healthcare products Regulatory Agency (MHRA) needs substantial revision particularly in relation to adverse event reporting and medical device regulation. It needs to ensure that it engages more with patients and their outcomes. It needs to raise awareness of its public protection roles and to ensure that patients have an integral role in its work.	1.41 – 1.45, 2.114, 5.50, 5.110, 5.112, 5.115

Recommendation 7: A central patient-identifiable database should be created by collecting key details of the implantation of all devices at the time of the operation. This can then be linked to specifically created registers to research and audit the outcomes both in terms of the device safety and patient reported outcomes measures.	1.46 – 1.49, 2.98, 2.115, 5.14, 5.50
Recommendation 8: Transparency of payments made to clinicians needs to improve. The register of the General Medical Council (GMC) should be expanded to include a list of financial and non-pecuniary interests for all doctors, as well as doctors' particular clinical interests and their recognised and accredited specialisms. In addition, there should be mandatory reporting for the pharmaceutical and medical device industries of payments made to teaching hospitals, research institutions and individual clinicians.	1.50 – 1.53, 2.56, 2.58, 2.65
Recommendation 9: The Government should immediately set up a task force to implement this Review's recommendations. Its first task should be to set out a timeline for their implementation.	1.54-1.55, 2.42, 7.3-7.5

Actions for Improvement

Chapter 2 – Overarching themes	
Theme 3: Informed consent	
Information should be conveyed to patients in a way that is clear and meaningful. The opportunity to speak to, or hear from, others who have undergone the same intervention should be considered.	2.21
A single patient decision aid (or core set of information) should be produced for each surgical procedure or medical intervention, co-designed by patients and clinicians. The National Institute for Health and Care Excellence (NICE) should take the lead on facilitating this.	2.22
Patient-clinician consultations about consent must be proportionate to the circumstance and appropriately documented. Both the patient's and clinician's concerns and comments should be recorded. Where appropriate and with the agreement of both parties, conversations around consent should be audio or video recorded to allow the patient to take it away and reflect upon it. In future a copy of this discussion should be stored on the patient's electronic record.	2.24

Theme 4: Redress	
There is a need for additional training for those carrying out assessments for DWP based on the insight condition reports. This should help those carrying out the assessments to make equitable decisions.	2.28
Theme 5: Complaints	
Patients across the NHS and private sector must have a clear, well publicised route to raise their concerns about aspects of their experiences in the healthcare system. It will be for the implementation task force (see Recommendation 9) to address this problem.	2.42
The time bar on GMC investigations should not be a barrier to establishing a pattern of poor practice by any one clinician.	2.43
The bodies that have received complaints about the interventions under review should reassess what they have been told and satisfy themselves that they have taken necessary steps to identify any patterns and trends. They should inform the relevant organisations and Patient Safety Commissioner of outcomes of concern.	2.44
Organisations who take complaints from the public should designate a non-executive member of the board to oversee the complaint handling processes and outcomes, and ensure that appropriate action is taken.	2.45
Theme 7: Conflicts of interest	
Organisations: Organisations should ensure clear governance arrangements to cover the potential conflicts of interests of any individual who participates in either regulatory activities or inquiries, including the composition of expert panels. Whilst it is to be expected that those people asked to participate should declare any potential conflicts of interest, the organisation itself has a responsibility to make its own enquiries.	2.64
Research: All journals should provide assurances to their readers that their Code of Practice relating to Conflict of Interest is compliant with the policy set out by the World Association of Medical Editors.	2.67
Theme 8: Guidelines: implementation and assurance	
Annual appraisal of doctors should include providing evidence of awareness of relevant guidance in the doctor's area of practice. Colleagues should report failure to follow guidance which is detrimental to patient safety. This should apply in the private or independent sector as well as in the NHS.	2.69
The GMC should be alert and act, if any doctor's practice causes concern in respect of failure to follow guidance.	2.70

Hospitals should encourage clinical audit and should have robust systems for monitoring quality at Board level. The Care Quality Commission (CQC) should also assure itself that hospitals both in the NHS and in the private sector, have robust quality assurance programmes including following appropriate guidance.	2.71
Those responsible for introducing new procedures should factor in the particular responsibilities of clinicians and organisations to monitor risks during this period, including the training time taken to acquire the necessary competencies and skills.	2.74
When the system has monitored guidance or standards, and identified an issue, there must be clarity on who is responsible for co-ordinating action, and sufficient support and resource for implementation of remedial action.	2.77
Theme 9: Collecting and using data	
Patient reported measures such as Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) should become common currency in the assessment of the benefits and risks of current and new interventions.	2.81
Every interaction the patient has with a health service provider should be captured once only and by one or other data subset, ideally in the electronic health record. The NHS number should be included to enable those subsets to be linked.	2.82
Every child's NHS number should be entered on their school attainment record on year of entry.	2.84
Theme 10: Databases and Registries	
Databases and subsequent registries should embrace the private or independent health care sector as well as the NHS.	2.91
Theme 11: Regulation	
When making regulatory decisions on benefit and risk of medicines and medical devices, the MHRA should demonstrate how patient views have been taken into account.	2.107
To aid public understanding the MHRA should give detailed reasons for its decisions if they differ from decisions made by another major international regulator.	2.112
The Department for Health and Social Care (DHSC) should consider if an equivalent of the Commission on Human Medicines (CHM) is needed for devices.	2.114
Where the patient gives permission an adverse device report should be linked to the patient identifiable database of implanted devices.	2.115

A public facing Unique Device Identification (UDI) database for UK devices based on the Global Unique Device Identification Database (GUDID) should be scoped.	2.116
We recommend a publicly searchable database of adverse events for both medicines and devices.	2.121
In future we recommend careful consideration should be given to implementing risk mitigation strategies of international regulators on potential teratogens.	2.123
We recommend the creation of a system-wide healthcare intelligence unit to facilitate early signal detection which would draw on various sources of information.	2.126
Chapter 3: HPTs	
The MHRA and CHM need to review their Expert Working Group (EWG) processes, specifically: • whether they should consider proactively checking potential members' interests prior to their appointment; • how to best support the involvement of affected and other lay individuals in EWG meetings, including both asking and answering questions at appropriate points of the meeting; • whether an independent secretariat should be used for EWGs; • whether EWG reports should be reviewed by an independent panel of experts.	3.103, 3.105, 3.112, 3.118
Chapter 4: Valproate	
An indicator on safe prescribing in pregnancy should be introduced for future iterations of the Quality and Outcomes Framework (QOF).	4.64
In our view, a clear process should be agreed to ensure women are able to get appropriate counselling related to their epilepsy treatment and contraceptive choices.	4.75
Information should be collected to identify those already affected by exposure to valproate in utero to ensure they have access to diagnosis and support, and to plan service provision.	4.90
A prospective registry should be established for all women on anti epileptic drugs who become pregnant, to include mandatory reporting of data relating to them and their child(ren) collated over lifetimes. This registry could potentially be expanded to collect data on paternal and transgenerational effects.	4.91 -4.92

The relevant stakeholders should continue to work with patient groups to monitor and improve the Pregnancy Prevention Programme and to consider the next steps, which should include NHS England and NHS Improvement (NHSE&I) writing directly to all women and girls of childbearing potential, asking them to see their general practitioner or specialist.	4.94 – 4.97
Clinicians should continue to follow guidance regarding prescribing of valproate and alternatives for all indications.	4.99
A system similar to the Pregnancy Prevention Programme should be used where teratogenicity is well-known or the effects are severe. Alternatively an acknowledgement of risk form should be attached to the prescribing and/or dispensing of all medication considered to have teratogenic potential or known to have a risk above that of the general population.	4.106
Chapter 5: Mesh	
Further research is urgently needed so that a clearer view can be reached on the inherent properties and safety of pelvic mesh.	5.33
Medical device manufacturers must research and develop a remedial strategy to address any severe complications caused by their product. This strategy should be set out in the Instructions for Use (IFUs) and guidance. The strategy should be developed collaboratively with appropriate input from others, such as the regulators and the commissioners of any services required to carry out actions.	5.38
We recommend that when a device or procedure is introduced a cohort of early recipients undergo enhanced reporting to detect unexpected adverse impacts.	5.52
NICE's most recent guidance states that the Transvaginal Tension Free Vaginal Tape-Obturator (TVT-O) should not be offered routinely. In the future, we feel the TVT-O should only be used in exceptional circumstances, if at all.	5.55
Professional bodies should lead on ensuring surgeons only operate within their capabilities. They must provide guidance for their members and ensure that surgeons are appropriately trained, and this should be assured through the appraisal process.	5.56
A culture must exist where all multi-disciplinary team (MDT) members feel able to speak up and that their input will be listened to. Trusts must work to create a culture that facilitates effective MDTs.	5.58

Conservative measures must be offered to women before surgery. We have heard that specialist pelvic floor physiotherapy cannot match the current demand. The service commissioner should identify gaps in the workforce and notify specialist clinicians, professional organisations and Royal Colleges. A co-ordinated strategy can then be developed to remedy the gap.	5.59
Clinicians must ensure patients have sufficient understanding of their treatment including the benefits, the potential risks it presents, and the alternative treatment options, including doing nothing, in order to decide whether they are willing to have that treatment.	5.60
Clinicians need to establish and agree terminology and definitions related to both mesh insertions and removals.	5.68
An audit to establish complication rates should be attempted using the women who had mesh insertions in 2010.	5.87
A consensus needs to be reached on whether it is better to carry out full or partial removals. This is a clinical matter, and it must be done collaboratively, including consulting international experts. This consensus should be validated by carrying out follow up on those who have removals at the specialist centres. We strongly recommend that NICE actively monitor the situation and update their guidance promptly once a consensus has been reached.	5.95
Consideration should be given to credentialing a small number of centres and surgeons for particular complex pelvic mesh surgeries.	5.102
A remote counselling service along the lines we set up during this Review should continue to exist.	5.105
Pelvic floor education should be encouraged, where appropriate, in schools and certainly in antenatal classes. In addition, we recommend that the NHS adopts the French model for universal post-natal pelvic floor rehabilitation.	5.123
Dismissive, defensive attitudes by surgeons are a cultural issue that needs to be addressed by the medical profession, its professional bodies and regulators.	5.124

Appendix 1: Terms of Reference

Background to the Review

In February 2018, the former Secretary of State for Health and Social Care, the Rt Hon Jeremy Hunt MP, announced a review into how the healthcare system in England responds to reports from patients about harmful side effects from medicines and medical devices. The announcement in the House of Commons followed patient-led campaigns on the use of the hormone pregnancy test Primodos, the anti-epileptic drug sodium valproate for women and girls of child bearing age and pelvic mesh. The Review will be chaired by Baroness Julia Cumberlege and will be independent of the Government, NHS, regulatory and other public bodies, and the pharmaceutical and medical devices industries.

A report of the Review's work will be published.

Scope of the Review

The purpose of the Review is to make recommendations for improving the healthcare system's ability to respond where concerns have been raised about the safety of particular clinical interventions, be they medicines or medical devices.

The Review will assess the historic evidence relating to the science of what was known, (in the case of Primodos during its lifetime and now, and in respect of sodium valproate and pelvic mesh up to the current date) and the decision making and actions taken, based on that scientific knowledge, by the manufacturers, regulators, clinicians and policy makers. If there appear to be flaws in the gathering of that scientific evidence, or questions over its independence or interpretation, the Review will comment accordingly.

The Review will also consider the practice of obtaining patients' consent to each of the three clinical interventions, historically in the case of Primodos, and up until the present day for sodium valproate and pelvic mesh, including appropriate practice (taking into account the historical context) in explaining to patients the potential benefits and the associated risks of any intervention.

The Review will focus on whether the processes pursued to date, when safety concerns have been raised by patients, their families and others, have been sufficient and satisfactory in relation to Primodos, sodium valproate and pelvic mesh.

In each of the three areas, the Review will investigate:

- the robustness, speed and appropriateness of those processes and actions followed by the relevant pharmaceutical/medical device manufacturers and applicants for and holders of licenses to manufacture and sell pharmaceutical products and medical devices, the regulatory authorities, healthcare providers, public and clinical bodies and policy makers;
- whether problems could have been recognised by the relevant bodies, authorities, manufacturers and license holders and others sooner and more effectively;
- whether the same bodies could, and should, have acted upon concerns sooner and if they did not, the reasons why.

In all its work, the Review will consider, and take account of, the historical context, including the requirements of any regulatory or licensing regimes for medical devices and medicines in force at the appropriate times.

In addition to the above, there are questions of interest to the Review in relation specifically to:

A) Primodos

- i. where the science is not broadly acknowledged or accepted, whether the available historic and scientific evidence (and its assessment to date) can reasonably preclude ‘a possible association’ between Hormone Pregnancy Tests and their teratogenic effects, and/or needs to be revisited, in the opinion of the Review;
- ii. given the knowledge on Hormone Pregnancy Tests available to the manufacturers, regulators and clinicians at the time, the consideration, advice and practice with regard to the use of alternative, non-invasive pregnancy tests.

B) Sodium Valproate

- i. the circumstances of the pharmaceutical licensing of Sodium Valproate and treatment to date for women and girls of child bearing age based on the growing body of agreed scientific evidence as to its teratogenicity;
- ii. how that scientific knowledge was, or should have been, communicated between the manufacturers, regulatory authorities, clinicians and patients and subsequently acted upon;

- iii. whether a consensus has been reached on defining the characteristics of the conditions referred to as Fetal Valproate Spectrum Disorders and the implications of this for proper diagnosis and assessment of the lifetime needs of those affected.

C) Abdominal and vaginal pelvic mesh procedures⁵⁰³

- i. whether the scientific evidence underpinning current regulatory and clinical practice fully and properly reflects:
 - a. the long term quality of life impact where there are adverse complications following these pelvic mesh procedures;
 - b. the innate properties of the polymeric material currently in use in the manufacture of pelvic mesh products and what is known about how those properties change once the mesh has been implanted in the human body and over time; and
 - c. the risks associated with the procedures themselves in comparison with the alternative available options.
- ii. the circumstances of the synthetic pelvic mesh medical device regulation, approval and adverse effects reporting to date.

It is not the intention of the Review to re-do the work recently undertaken by other Reviews/Expert Working Groups into each of the three interventions here and in other jurisdictions. The Review will, however, take account of them in addressing these questions and in developing their narrative from the perspective of the healthcare system's response to patients' safety concerns raised over time.

The Review recognizes that, over time, there is likely to have been significant differences in the quality and robustness of the evidence bases that support the use of medicine and medical device technologies. Taking this into account, the Review will make recommendations on what should happen in future in relation to Primodos, sodium valproate and pelvic mesh, including:

- whether further action is now required;
- what that action should consist of; and

⁵⁰³ These include treatment for stress urinary incontinence (SUI) and abdominally inserted pelvic organ prolapse (POP) procedures including for example (but not limited to) sacrocolpopexy, hysteropexy and rectopexy. We recognise that vaginally placed mesh for POP has been restricted to research only since December 2017.

- whose responsibility it is to act.

These recommendations will be specific to each of the three clinical interventions and the patient groups affected and will reflect their different needs and the issues they face.

The Review will consider and make recommendations more broadly, based on its assessment of any lessons to be learned, on what could be done in the future to:

- identify and acknowledge problems with medicines and medical devices effectively and quickly;
- strengthen the voice of patients and their families and others, so that their concerns are heard in an open, fair and accessible way;
- ensure that those concerns are recognized and acted upon appropriately, as swiftly as possible and in a coordinated fashion; and
- ensure that those adversely affected receive the care and support they need.

The Review may make additional recommendations that bear on the healthcare system's response to, and responsibility for, patient safety issues, having considered the effectiveness of the relationships between those public bodies and commercial interests that have a role to play in bringing safe medicines and medical devices to market, in post-marketing surveillance and in responding speedily and appropriately to safety concerns when they need to. Whilst not seeking to redesign the regulatory framework, the Review may comment on aspects of it, including how the reporting of patient safety concerns may be improved.

The Review will not undertake, or otherwise commission, new evidence in relation to the science behind each of the three clinical interventions, although it may make recommendations to that effect.

Nor will the Review's work include consideration of whether, or how much, compensation may be due to an individual who has suffered harm.

It will, however, consider whether as a priority a wider system of redress, including forms of care and support, should be developed. The Review may make recommendations on any forms of redress, including recommendations as to whether there is a moral, social or ethical responsibility to consider a system of compensation, if it concludes that there has been avoidable harm suffered as a result of the medical interventions it has considered, or any of them. It will not make findings upon whether, in an individual's case, such harm has been suffered.

It may also make recommendations on the proper and fair processes that should be followed, either in these three cases or others in the future, to ensure public confidence in the healthcare system, its decision making and practice, is maintained and strengthened.

Approach

Our Review will listen, learn and recommend.

We will listen to those who have suffered harm. Their voices, their experiences and views will be at the heart of our Review.

We will also take evidence from regulators, NHS bodies, health professions, healthcare providers, manufacturers, suppliers and others to understand what happened, how they have responded to the concerns raised and what they think needs to happen.

We will seek to learn from the three cases so that we can form our own independent and objective views on what has happened and make recommendations about what needs to happen now.

The Review will not seek to determine, and has no power to determine, any person or body's civil or criminal liability. But it will seek to examine processes and safeguards designed to avoid harm to patients, and whether they were effective.

Where safety concerns leading to avoidable harm do arise in future, we will seek to ensure that those affected are heard and supported in a swift and sensitive manner and the appropriate, co-ordinated response processes are identified.

We will make ourselves accessible so that we can hear as many views and experiences as possible. We will use meetings, events, correspondence and social media to facilitate this.

We know that many people will take an interest in our Review and be keen to know our conclusions. We cannot at this stage indicate when the Review will report but we undertake to work with all due speed and thoroughness.

Appendix 2: The Patient Safety Commissioner

This paper outlines the need for a Patient Safety Commissioner and describes the form and function this role could take.⁵⁰⁴

1. The Commissioner would be an independent and proactive public leader with a statutory responsibility to champion the value of listening to patients and promoting users' perspectives in seeking improvements to patient safety. S/he would sit outside the current patient safety system and have a direct line of accountability to Parliament through the Health and Social Care Select Committee. Through her/his work, the Commissioner would identify steps that need to be taken to improve patient safety around the use of medicines and medical devices and encourage other organisations to act. S/he would provide a means of holding the current system to account on behalf of patients for delivering necessary improvements in patient safety.

What is the problem?

2. We, alongside other inquiries into safety and quality issues in healthcare, have repeatedly demonstrated that when patients and their families have identified and reported harms, these reports have not been acted on until forced into public attention by campaigns or media interest.
3. Patients are important partners with health professionals and NHS bodies in promoting safety and identifying risks of harm. Too often patient and family voices have been ignored even though they were right. It should not be left to patients or their families to join up the dots of patient safety.
4. In our view serious harm is being done to patients and their families as a result of failure to identify risks in a timely manner or to respond to identified risks with appropriate action. Patient reports of harm may be dismissed as subjective, unscientific and anecdotal, particularly if they cannot be accommodated by existing reporting systems. While some improvements in patient involvement and engagement in the patient safety system have been delivered, the evidence gathered through the Review indicates that there is room to do more to tackle the burden of avoidable harm.

Mapping the current system

5. Any solution to the issues identified needs to avoid duplication of current structures and approaches and seek to improve patient safety in an innovative manner. It needs to be able to vigorously promote the patient and public perspective, and to be active in seeking improvements to patient safety.
6. Oikonomou E, et al (2019)⁵⁰⁵ provides a useful summary for mapping the current system of organisations involved in patient safety. The authors identify 126 organisations with ‘some regulatory influence’ on NHS providers in England, with (at time of the paper’s writing⁵⁰⁶) an additional 211 NHS commissioning bodies. In their analysis, the authors identify these as either regulators or organisations with a regulatory effect. The paper defines 15 different ‘overseeing functions’ in patient safety regulation. Of these, the following are directly involved in tackling patient safety concerns about medicines and medical devices:
 - a. Monitoring of services and professionals – systematic collection of information to assess and maintain standards of care
 - b. Research – systematic investigation of events and information relevant to maintaining standards
 - c. Investigation – formal examination of an incident
 - d. Inspection – formal examination or visit to assess standards of care
 - e. Analysis and sharing of data – collection of data, analysis and potentially sharing with other regulatory organisations
 - f. Advice and support for healthcare providers or other regulators – providing professional or legal advice to professionals and organisations
 - g. Advice and support for the public – publishing performance evaluations or other information on standards
 - h. Standard setting
 - i. Policy provider – setting formal rules and guidelines.

⁵⁰⁵ Oikonomou E, et al. 2019 *Patient safety regulation in the NHS: mapping the regulatory landscape of healthcare*. *BMJ Open*. 9:e028663.

⁵⁰⁶ Note that Oikonomou E et al (2019) does not include the Healthcare Safety Investigation Branch in its detailed analysis.

7. Using data in the paper, it is possible to build a summary map of the delivery of patient safety regulatory activities by organisation. In Table 1, the nine regulatory activities listed above, relevant to the different stages of tackling patient safety issues, are mapped and the organisations that undertake each activity are noted.
8. This mapping shows that there is a tremendous number of opportunities to improve patient safety, across a wide range of organisations. At the same time, as we have shown, it is a crowded landscape that can stand in the way of timely responses to concerns about patient safety. An individual organisation can work well, but the linkages between different parts of the system do not work as successfully.
9. Existing patient safety reporting schemes and approaches (such as MHRA's Yellow Card Scheme, NHS Improvement's (NHSI) National Reporting and Learning System and the Healthcare Safety Investigation Branch (HSIB)) receive reports from the public and patients and use these to inform reviews. Each organisation will use its own particular technical specialism and perspective to tackle the patient safety issues it encounters. These specialisms and perspectives will in turn influence how solutions are developed and implemented. For example, NHSI focuses on delivering skills and programme improvements within the NHS; the Medicines and Healthcare products Regulatory Agency (MHRA) focuses on better regulation of safety and quality of medicines and devices; HSIB focuses on incident investigation. All three will use patient reporting to inform in their safety work, and all involve patients and the public as stakeholders in their expert reviews, and in their governance structures.
10. While these approaches make arrangements for patient and public involvement, this is alongside other parties and stakeholders and within existing methodologies. As seen by the examples in this Review, this does not deliver the systemic improvements that long-standing safety concerns have indicated are necessary to protect future patients from avoidable harm in the future.

Table 1: Mapping delivery of patient safety regulatory activities (English NHS)

Based on Oikonomou E, et al (2019)

Identification of an issue	Investigation of an issue	Identification of a solution	Implementation of solution
Monitoring of services and professionals CQC, NHSI, HFEA, EA, Commissioners, MHRA, Info & Standards, Advisory Groups	Investigation CQC, NHSI, HFEA, HSE, EA, Coroners, HTA, MHRA, Prof Regulators, Commissioners, Info & Standards, Peer Review, Advisory Groups, Royal Colleges	Advice and support for healthcare providers or other regulators NHSI, HFEA, EA, NHS Resolution, HTA, Info & Standards, Peer Review, Advisory Groups	
Research HFEA, HSE, Coroners, HTA, MHRA	Inspection CQC, HFEA, HSE, EA, HTA, MHRA, Prof Regulators, Commissioners, Info & Standards, Peer Review, Advisory Groups, Royal Colleges	Advice and support for the public CQC, NHSI, HFEA, HSE, NHS Resolution, HTA, MHRA, Prof Regulators, Info & Standards, Advisory Groups	
	Analysis and sharing of data CQC, NHSI, HFEA, MHRA, Prof Regulators, Commissioners, Peer Review, Advisory Groups		Policy Provider CQC, NHSI, HSE, EA, HTA, MHRA, Prof Regulators, Info & Standards, Royal Colleges
			Standard Setting CQC, UKAS, HSE, EA, HTA, MHRA, Prof Regulators, Commissioners, Info & Standards, Royal Colleges

Notes:

- the professional regulators have been grouped together
- the paper does not consider that the MHRA undertakes monitoring of services or professionals
- The authors identified NICE as an organisation with a regulatory effect and grouped under 'Info & Standards'.

What needs to change?

11. Through our work, we have identified three broad areas for improvement in the management of issues and concerns about patient safety:
 - a. There needs to be more widespread and timely recognition by the patient safety system of issues identified by patients and the public
 - b. The patient safety system needs to get better at listening to and acting on patients' experiences of avoidable harm
 - c. There needs to be swifter and better coordination across and between agencies when improvements and solutions are identified, for the sake of future patients and other members of the public.
12. There is a need to formally recognise and promote the value that direct patient reports about safety concerns can have on improving the safety of healthcare. The Review has shown how working from this perspective can bring swift and timely action to reduce avoidable harm (e.g. surgical mesh and sodium valproate).
13. Patients' experience should be at the centre of the patient safety system and a measure of its overall success. If there is to be a step change in tackling avoidable harm, this fundamental perspective on patient safety can no longer be systematically overlooked.
14. Our findings provide an opportunity to take an innovative and complementary approach to improving patient safety: a new way of working that sits apart from existing structures and arrangements, drawing on the experiences of patients and bringing vital insight to safety issues, while driving action and accountability for timely and systemic improvements in the delivery of care, wherever they are needed.

The Patient Safety Commissioner

15. The Patient Safety Commissioner fulfils the needs we have identified. The role will bring a unique and focused perspective to efforts to improve patient safety that complements the work of current organisations and agencies, while also addressing the concerns identified around the timeliness and coordination of action on concerns that patients have repeatedly raised. It offers the opportunity to build directly from patients' experience and to secure systemic improvement.
16. This recommendation emerges from a study of parallels in other sectors. The Children's Commissioner for England was established '*to ensure children's and*

young people’s voices are effectively heard’ and to ‘act as a children’s champion independent of Government’⁵⁰⁷. In overseeing a complex system on behalf of its users, the Commissioner proposal also has parallels with bodies such as the Professional Standards Authority (PSA) for Health and Social Care and the Legal Services Board.

17. As an independent champion of the voice and experiences of patients and other members of the public on safety concerns, the Patient Safety Commissioner would have two aims: to improve identification of systemic safety issues and to improve the system’s coordinated response. Through a renewed focus on patients’ needs and a drive for cooperation and coordination, the Commissioner will help to release the wider benefits for the healthcare system from individual organisations’ safety improvements.

The Commissioner’s functions and activities

18. The primary statutory function of the Patient Safety Commissioner would centre on the aims of:
 - promoting and improving patient safety, and
 - promoting the views and interests of patients and other members of the public in relation to the safety of medicines and medical devices.
19. The Commissioner’s role would be designed to operate flexibly and prioritise her/his work so that they do not duplicate activity being undertaken elsewhere in the system, while also advising and recommending actions where they are needed.
20. The Commissioner’s primary function could be delivered in several ways. Some would be laid out in legislation, but this list would be complemented by a general power to do anything which appears to be necessary for the exercise of the functions.
21. The Commissioner would set her/his own priorities and determine the appropriate response. This would be based around a core set of statutory **Principles of Better Patient Safety** that the Commissioner would be required to develop (see below), and informed by direct reporting, horizon scanning, commissioned research and data analysis.

⁵⁰⁷ Every Child Matters para 5.50.

22. The Commissioner's response to a specific issue would be determined on a case by case basis by reference to the Principles, but could be expected to lead to **reviews and investigations** that result in advice and recommendations. Reviews could include:
- thematic investigations of systemic issues
 - in-depth inquiries into specific patient safety concerns, where not undertaken by another organisation
 - assessments of an organisation's patient safety performance, against the Principles of Better Patient Safety.
23. The nature of the Commissioner's **advice** arising from reviews and investigations could take a range of forms:
- specific recommendations to address identified patient safety concerns
 - encouraging implementation of recommendations by other bodies
 - highlighting concerns about delays and failures to act to improve patient safety, through reports to the Health and Social Care Select Committee, to the Secretary of State for Health, to other agencies and organisations, and in public reports.
24. The Commissioner would be open to **receiving direct reports from patients and other members of the public**. The Commissioner would also forge links with organisations representing patients. This broader remit would allow related third-party reporting, for example by family members, such as parents. It would also demonstrate that the Commissioner had a remit for those who did not necessarily see themselves as 'patients' (for example pregnant women). While this would allow some duplication of reporting this would not be unreasonable given the problems we have identified. Given her/his role, the Commissioner is expected to have a higher public profile than other bodies who receive patient safety reports directly from the public. Arrangements could be made to relay direct reports received by the Commissioner's Office to those organisations as appropriate. The Commissioner would retain an interest in how reports are handled, including in patterns in reporting and their outcomes.
25. Legislation would prevent the Commissioner from investigating individual cases, as this would duplicate the work of the Parliamentary and Health Service Ombudsman. Provision would be made in legislation for the Commissioner

to act on broader issues highlighted by an individual incident (as for the Children’s Commissioner⁵⁰⁸).

26. The Commissioner would be able to **obtain relevant information** relating to patient safety concerns from other organisations, giving the Commissioner the responsibility to actively seek the relevant data and information from others to inform and deliver their primary functions. This would include making arrangements to receive reports relating to the safety of medicines and medical devices from the National Guardian (Freedom to Speak Up). The Commissioner would also have arrangements for receiving reports from whistle-blowers.

Principles of Better Patient Safety

27. The Principles of Better Patient Safety will be at the heart of the Commissioner’s work. The Principles will be a succinct description of the patient safety system outcomes that matter for patients and other members of the public.⁵⁰⁹ The Principles will subsequently form the basis for the activities undertaken by the Commissioner, through reviews and investigations, advice and recommendations, in research, and in advocacy work in the wider patient safety community.
28. Other bodies with a role in patient safety have identified principles. For example, in 2019, NHS Improvement’s Patient Safety Strategy adopted three principles of Insight, Involvement and Improvement⁵¹⁰. These complement the Commissioner’s statutory principles, which will explicitly focus on promoting the voice of patients and other members of the public to improve the safety of medicines and medical devices and be embedded throughout the Commissioner’s work.
29. It is inappropriate to prescribe the Principles here. The Commissioner’s first act would be to work with patients, the public and their representatives to co-create and develop the Principles, and subsequently consult and finalise with the wider patient safety community. However, it is expected that the Principles will address the problems identified by this Review, including the failure to listen to patients and lack of timely and coordinated responses across the system, to describe the outcomes that matter for patients and other members of the public. For example:

⁵⁰⁸ A similar provision is made for the Children’s Commissioner by Section 3 of The Children’s Act 2004.

⁵⁰⁹ This proposal mirrors approaches of other independent oversight bodies. For example, the Professional Standards Authority has a general function to promote the interests of patients and is subject to a requirement to (among other things) demonstrate this general function through its statutory function of ‘the formulation of principles relating to good professional self-regulation’. For the Children’s Commissioner, the UN Convention on the Rights of the Child (UNCRC) provides a core set of values that performs a similar (but not identical) role. The Legal Services Board is bound by eight statutory regulatory objectives.

⁵¹⁰ The NHS Patient Safety Strategy July 2019.

Examples of potential Principles of Better Patient Safety

For me, as a patient, a better patient safety system is one that is seeking to reduce avoidable harm by:

- involving me in my care
- being open about the treatment choices I have
- listening to my concerns and experiences
- improving wherever possible
- cooperating and coordinating as it responds to emerging issues.

Engagement with patients and the public

30. Given the fundamental importance of patient experience to the work of the Commissioner, meaningful and effective engagement of patients and other members of the public in the Commissioner's operations will be essential to securing legitimacy for the reviews, investigation and advice.
31. The Patient Safety Commissioner's work would be underpinned by a number of engagement and involvement activities. The Patient Safety Commissioner would be required by statute to appoint an **Advisory Board**. The Board's role would be to provide advice and support to the Commissioner as they delivered their statutory functions. The Board's precise terms of reference and appointment criteria would be established by the Commissioner but would need to reflect the two primary statutory objectives.
32. The Commissioner would also be required to operate under a **statutory duty to involve and inform patients and other members of the public**. It would be for the Commissioner to account for how this duty is met. It would be expected that the Commissioner would consider a range of different approaches including commissioned research, reference panels for reviews and investigations, and public consultations. This would be in addition to encouraging direct patient reporting to the Commissioner's Office on issues and ongoing analysis of the themes that emerge from these reports.

The Commissioner's powers

33. In common with other similar roles, the Commissioner would have a general statutory power *'to do anything which appears to it to be necessary or expedient for the purpose of, or in connection with, the performance of its functions.'*⁵¹¹ This would give the Commissioner the power to take a permissive and flexible approach to gathering information necessary for specific issues and to issue advice to those who are engaged in activities relating to improving patient safety. Giving the Commissioner the power to bring matters to the attention of both Houses of Parliament and the Secretary of State for Health and Social Care would provide a proportionate and focused means of highlighting where improvements are needed.⁵¹²
34. Based on the evidence we have gathered, it is not proposed at this point to give the Commissioner more wide-ranging regulatory powers to bring about change. The Commissioner's role is explicitly that of a champion, seeking to amplify the voice of patients and deliver timely and coordinated systemic improvements in patient safety.

Appointment and accountability

35. The Patient Safety Commissioner would be, as with similar roles, a Statutory Office Holder. Given the remit for the Commissioner, it would be expected that the Secretary of State for Health and Social Care would play a role in their appointment. However, this may risk the need for the role to be demonstrably independent from the current healthcare system. That being so, it would be preferable for the role to be appointed by the Privy Council (as with the health professional regulators and the PSA⁵¹³).
36. The Commissioner's term of office would be prescribed by legislation and will need to be long enough to enable progress to be made. Given the functions outlined above, and the likely need to conduct in-depth reviews of specific issues, the term of office would be expected to be four years, with an option of a single extension of two years if circumstances require it.
37. The Commissioner would be free to look at whatever they wish to within her/his remit of patient safety, open to requests for areas to consider and free to publish their findings. The Commissioner would be accountable to the Parliamentary Health and Social Care Select Committee. Alongside annual hearings and using the power to bring matters to the attention of the Committee, the Commissioner could receive and act on information and requests from the Committee, and from the Secretary of State for Health.

38. The Commissioner's work would be supported by grant-in-aid funding from the government.^{514,515} Again, the importance of demonstrating and maintaining independence from the current system strongly suggests that the Commissioner's funding and sponsor relationship should come through the Cabinet Office, rather than the Department of Health and Social Care.

Organisational structure

39. It would be for the Commissioner to determine how her/his office was structured to meet its statutory functions. In doing so, there would be a clear need for the Commissioner to balance the resources available to her/him with the need to support and enable easy access for patients, the wider public, health professionals and organisations to interact with the Commissioner across a range of platforms. Alongside a central corporate services function (for governance, administration, human resources, finance, legal), one possible approach would be as follows⁵¹⁶:
- Research and Analysis – receiving direct reports, horizon scanning, data processing and analytics
 - Policy and Investigations – Principles of Better Patient Safety, thematic reviews, specific investigations, developing Commissioner's advice
 - External Relations – advocacy, communications and media, parliamentary liaison, stakeholder relationship management
40. In the short-term we might expect the Commissioner to focus on:
- Developing, consulting and agreeing the Principles for Better Patient Safety
 - Developing and implementing a data and analytics strategy, including horizon scanning, policy on use of specific powers, handling direct reporting, signposting and referral arrangements for individual patient's concerns
 - Developing a prioritisation framework to enable transparent selection of topics for review, investigation and advice
 - Building relationships and ways of working with key stakeholders in Parliament, government and the healthcare system
41. Having agreed and established the Principles, and with a full complement of staff, the medium term could see the Commissioner carrying out a system-wide assessment of current performance against the Principles, identifying priority areas for the Commissioner to focus on.

42. This work could be complemented by developing thought leadership and advocacy work around the Principles of Better Patient Safety and promoting the views and interests of patients. This area of activity could also include commissioning research.
43. Through this work, and in the longer term, the Commissioner will demonstrate her/his value in championing the voice of patients and other members of the public in improving patient safety and reducing incidence of avoidable harm across the healthcare system.

Appendix 3: Redress

Introduction

1. Our terms of reference encompass recommending whether redress should be provided, both for the interventions we have reviewed and more widely for future iatrogenic⁵¹⁷ harms. We have examined various redress mechanisms and have heard both informally and formally in oral and written evidence from those affected on the unmet needs they have. We have heard from various organisations with expertise in providing financial support after iatrogenic injury, including the Thalidomide Trust,⁵¹⁸ the vCJD Trust⁵¹⁹ and the Department for Work and Pensions⁵²⁰ on ways to deliver redress, and we have utilised expertise within the Review Team itself.⁵²¹

Litigation over HPTs, Pelvic Mesh and Valproate

2. All three of the interventions we have examined have attracted some litigation. Legal actions may be brought on the basis of product liability⁵²² or clinical negligence.⁵²³
3. The Primodos litigation started in 1977 against Schering. In 1982 it was discontinued at the request of the claimants due to difficulties in establishing a causal link between HPT use and congenital abnormalities.⁵²⁴ Since then there have been various attempts to re-commence litigation.⁵²⁵ In August 2019, solicitors announced⁵²⁶ that they had sent letters before action to Bayer and Sanofi (who have taken over Schering and Roussel respectively) and the Secretary of State for Health and Social Care.
4. A valproate group action was launched in 2003 involving around 100 claimants: the fetal anti-convulsant syndrome or FACS litigation. We have heard from NHS Resolution⁵²⁷ that there were discussions as to whether claimants should litigate against doctors in clinical negligence or against the manufacturers under product liability laws. A product liability claim against Sanofi was pursued. In 2010 the FACS case collapsed very shortly before the trial when the Legal Services Commission withdrew legal aid funding from the claimants. This was because they had received a negative assessment of the prospects of success from an independent QC.

5. To date, in the UK pelvic mesh has not had a group litigation succeed on the basis of product liability; this contrasts with countries such as Australia and the USA.⁵²⁸ Johnson & Johnson recently reached a without liability settlement of £50 million for pelvic mesh in Scotland. We have heard from individuals compensated for an NHS doctor's negligence in inserting pelvic mesh, but the overall numbers of claims reported by NHS Resolution are very low in comparison to the number of operations and compared to the number of women we have spoken to.⁵²⁹

Redress for existing harms related to HPTs, pelvic mesh and valproate

6. We recommend that three schemes are set up to provide additional support to those who have been avoidably harmed by hormone pregnancy tests (HPTs), pelvic mesh and valproate, (Chapter 1, **Recommendation 4**).

The future

7. To date, litigation has not served the patient groups we have met well. In the future a more equitable way to deliver redress that truly works for patients must be developed. Even the best pre-market testing will not capture all adverse events that may occur in real world treatment with pharmaceuticals and medical devices. Individuals may be harmed by new products in ways that were not foreseen during development and testing. We must establish an effective redress mechanism for those who suffer avoidable harm or unforeseen drug or device injury.

Potential structures for administering redress

8. We have considered existing examples of *ex gratia* payments for iatrogenic injuries, such as the Thalidomide Trust, the vCJD Trust, the infected blood payments, vaccine damage payments. The infected blood payments in England were made from five separate entities, two not-for-profit companies and three charities. Each entity had different eligibility criteria for payments based on whether the claimant

⁵²⁸ In **Australia** the class action case *Gill v Ethicon Sàrl* (No 5) [2019] FCA 1905.

In the **US** there were Multi-District Litigations (MDLs) and Multi-County Litigations (MCLs).

MDLs included, MDL-2187 In re. CR Bard, Inc. Pelvic Repair System Products Liability Litigation; MDL-2325 In re American Medical Systems, Inc. Pelvic Repair System Products Liability Litigation; MDL-2326 In re Boston Scientific Corp Pelvic Repair System Products Liability Litigation; MDL-2327 In re Ethicon Inc, Pelvic Repair System Product Liability Litigation; MDL-2387 In re Coloplast Corp Pelvic Support Systems Products Liability Litigation; MDL-2240 In re Cook Medical Inc, Pelvic Repair System Products Liability Litigation

MCLs included Bard & Gynecare MCL in Bergen.

⁵²⁹ NHS Resolution written evidence.

- was a haemophiliac or not and whether he or she had been infected with HIV or hepatitis C. This was overly complicated and difficult for claimants to navigate.
9. To date, all such national schemes have developed in a piecemeal manner and have been issue specific. As a Review that spans three interventions we have occupied a unique position, with sufficient oversight to take a more strategic view.
 10. We have examined various international models for redress provision,⁵³⁰ including the pharmaceutical and patient injury schemes in the Scandinavian countries, the Accident Compensation Corporation (ACC) in New Zealand, Office National d'Indemnisation des Accidents Médicaux (ONIAM)⁵³¹ the French iatrogenic medical compensation scheme, and redress provided by the Pharmaceutical and Medical Devices Agency (PMDA) in Japan.
 11. Of particular interest to us was ONIAM in France.⁵³² ONIAM administers the valproate scheme. However, it is a standing structure that determines liability to pay, and in some cases administers, compensation for medical accidents, damage from mandatory vaccinations, pandemic H1N1 influenza vaccinations, blood products contaminated with HIV, blood products contaminated with hepatitis C, growth hormone contaminated with vCJD, benfluorex damage and valproate damage.
 12. Similarly, PMDA operates five adverse health effects relief schemes, two for infected blood compensation, a pharmaceutical adverse drug reactions scheme, a biologics adverse drug reactions scheme, and a scheme for SMON compensation⁵³³ see table A3.1.

Scheme	Eligibility	Redress payments source
HIV/AIDS	Infection due to contaminated blood	Government funding
Hepatitis C	Infection due to contaminated blood	Government funding
Drugs ADRs	Adverse effects of pharmaceuticals	Hybrid funding (25% pharmaceutical manufacturer, 75% state funding)
Biologics ADRs	Adverse effects of biologics	Hybrid funding (25% biologics manufacturer, 75% state funding)

⁵³⁰ See S Macleod and C Hodges *Redress Schemes for Personal Injury* (Hart Publishing, 2017) for summaries.

⁵³¹ Office national d'indemnisation des accident médicaux.

⁵³² C Bright and C Hodges Chapter 18 France: The ONIAM Scheme in S Macleod and C Hodges *Redress Schemes for Personal Injury* (Hart Publishing, 2017).

⁵³³ SMON is subacute myelo-optic neuropathy, an iatrogenic condition symptoms of which included paralysis, blindness, and even death. A Tokyo District Court ruled that SMON had been caused by the drug cloquinal.

SMON	SMON cases due to cloquinol	Litigation settlement from pharmaceutical companies and care provided by the state
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Table A3.1. Schemes operated by PMDA in Japan including their funding source.

A Redress Agency

13. We recommend having a single Redress Agency that administers multiple schemes. This has several advantages. It is simple for patients to access as there is one fixed point of contact. This structure enables flexibility to adapt and respond to situations as they arise. Rather than starting from scratch for each intervention there is a pre-established administrative structure, to which new schemes can be added.
14. There are various options for funding the Redress Agency: case fees, payments from those who contribute to the schemes or state-funding.
15. The Redress Agency should function as a stand-alone redress mechanism. We are not advocating that it should replace litigation. Its design, processes and function should reflect court expectations of what constitutes an acceptable alternative dispute mechanism. In the future, if it was accepted by the courts, it could also be used as an alternative dispute mechanism in advance of litigation.

A straightforward process

16. We believe we have a duty as a reasonable and fair society to make the redress process straightforward, easy to use and fair. Patients claim because they have been harmed and have suffered. Obtaining the redress that they are entitled to should not feel like a battle and should not cause further suffering. Litigation is adversarial, but obtaining redress does not have to be. The Redress Agency should operate on the ombudsman model. It will listen to both sides, investigate impartially, and reach a decision. The onus is not on the injured party to prove their case.

The approach to determining responsibility for harm – System-wide or individual culpability

17. In addition to working for individual injured patients, the new redress system must achieve something for the wider healthcare system. Any healthcare system should aim to eliminate avoidable harm. In our view an open, honest culture in which mistakes are learned and barriers to disclosure are removed is overdue and essential. Clinical negligence litigation, which is blame-based and tends to focus

on the actions of individual doctors, can inhibit disclosure. For decades it has been known that the majority of mistakes are system errors,⁵³⁴ yet litigation deals with the culpability of individuals. The fact that children continue today to be exposed to valproate in utero and their mothers are unaware of the risks is a systems failure. Litigation usually has to focus on the actions of an individual doctor or pharmacist.

18. A shift to a judgment based on systemic error aids open disclosure and prompt resolution.⁵³⁵ **We consider this shift from individual culpability (blame) to systems-based responsibility for harm (avoidable harm) as essential.** We advocate that ‘avoidable harm’ is used as it mirrors the successful change seen in New Zealand and also the schemes used in the Scandinavian countries. This reframes the approach to focus on whether the harm could have been avoided if the actions the system had taken had been modified.

Thresholds

19. Avoidable harm describes a systems-based approach to assess whether the system bears any responsibility for the harm or not. Different thresholds for assessing eligibility for redress can be applied within this systems-based approach. UK ombudsman schemes tend to use a ‘*fair and reasonable*’ test.⁵³⁶ Patient injury schemes in Sweden and Denmark use an ‘*experienced specialist*’ test, where a treatment injury is ‘avoidable’ if an experienced specialist would not have made it. An alternative is the ‘*reasonable care and skill*’ test. In the Scandinavian countries payments are made if an injury from a pharmaceutical was *unforeseen*: either it was not warned about in the product information or it was more severe than would have normally been expected.
20. The threshold used for eligibility for compensation is likely to vary between different schemes. It is not our role to prescribe this. However, what must be consistent for all schemes is a system-based approach to responsibility based on avoidable harm.

⁵³⁴ To Err is Human: Building a safer healthcare system. (Institute of Medicine, 1999).

⁵³⁵ When New Zealand moved from a blame-based threshold to an avoidable harm threshold when analysing medical injuries for compensation the time taken to reach a decision went from 5 months to 13 days. This is thought to be because doctors were more willing to cooperate when they were not being blamed. Manning J. Access to justice for New Zealand health consumers. J Law Med. 2010;18(1):178–94.

⁵³⁶ ‘Fair and reasonable’ can include taking into account: the relevant law and regulations; regulators’ rules and guidance and standards; relevant codes of practice; and, where appropriate, what would have been considered to have been good industry practice at the relevant time.

Scope of the Schemes

21. **The Redress Agency will administer financial redress from specific schemes, each with their own eligibility criteria and funding.** In this way the schemes can be targeted to the specific harms suffered and funded accordingly. For example, the devices scheme funded by device manufacturers would only deal with devices claims, not with claims for other harms, for example treatment injury, and there would be no cross-subsidisation.
22. **Schemes for future harm should provide meaningful, sufficient redress based on the extent of the injury suffered.** The support offered could be both financial and non-monetary. Consideration should be given to the interactions between payments from these schemes and the benefits and taxation systems.⁵³⁷

Schemes for Pharmaceuticals and Medical Devices

23. We recommend that the Redress Agency administers schemes akin to those seen in the Scandinavian countries and in Japan where financial assistance is provided following drug and device injuries. **These schemes could be funded by a mandatory levy paid by the medicine and device industries in order to place a product on the UK market.**

Schemes for patient injury

24. It is unreasonable to expect a patient with an injury from an implanted medical device to know if the injury is due to the device itself or the actions of the implanting surgeon. Therefore, we propose that the Department for Health and Social Care considers creating a fund for NHS treatment injuries. For example, a patient with a device-related injury lodges their claim with the Redress Agency, who investigate, and determine whether redress payments are due. If a payment is due the Agency will then consider whether payment should come from the devices scheme, the treatment injury scheme or be apportioned from both.
25. The Paterson report⁵³⁸ recommended the creation of an industry wide ‘safety net’ to cover patients if their clinician’s indemnity is not honoured. This could take the form of a scheme that is funded by a levy on private clinicians, similar to the Motor Insurance Bureau,⁵³⁹ that would be administered by the Redress Agency we

⁵³⁷ For example, see the provisions of The Social Security (Infected Blood and Thalidomide) Regulations SI 2017/870; The Thalidomide Children’s Trust (Application of Section 329AA of the Income and Corporation Taxes Act 1988) Order SI2004/1819.

⁵³⁸ *Report of the Independent Inquiry into the Issues raised by Paterson* (February 2020) available at <https://www.gov.uk/government/publications/paterson-inquiry-report>

⁵³⁹ <https://www.mib.org.uk/>

are proposing.⁵⁴⁰ Should private providers wish to they could, of course, set up a separate more comprehensive scheme for the Redress Agency to administer.

Conclusions

26. **We do not wish to remove the option to litigate, but we propose a Redress Agency should be created to supplement the current systems, (Chapter 1, Recommendation 3). We have recommended a Redress Agency should be set up on an avoidable harm basis which focusses on systematic failings, rather than blaming individuals. The Redress Agency would provide a standing structure to administer redress from schemes using a non-adversarial ombudsman style process. Each scheme would have specific eligibility and funding, without any cross subsidisation. A scheme should be established for medical devices and a scheme for pharmaceuticals, which could be funded by a levy on manufacturers.**
27. **The creation of the three separate schemes we are recommending for those affected by HPTs, valproate and pelvic mesh (Chapter 1, Recommendation 4) should not be delayed pending the establishment of the Redress Agency. They should however be structured so that they can be incorporated into the wider Redress Agency in due course.**

⁵⁴⁰ As part of the EU Directive 2002/13/EU governs the reserves that risk-pooled insurance schemes have to hold, as we leave the EU there is an opportunity to review the appropriateness of these reserves for this type of risk-pooled scheme, which may increase the affordability of this type of arrangement.

Appendix 4: How we Worked⁵⁴¹

Key Principles

1. From the outset our way of working has been governed by four key principles.
2. **First**, we adopted a ‘families first’ approach. We placed those most directly affected by the three interventions at the heart of our review process – a process that was designed to listen to the families, to understand their concerns and the reasons why they felt aggrieved. It was with the families and those campaigning on their behalf that we first shared major statements during the course of the Review. And it was with those same patient groups that we first shared our findings and recommendations at the end of the Review. We recognised, as other reviews and inquiries had done before us, that to do otherwise would only exacerbate the loss of trust felt by many of these families – a loss of trust that was in part the reason for prompting the Review.
3. It did not follow, however, that the Review was anything but totally objective in its rigorous analysis of the evidence we sought and received. The families affected would not have wanted this, nor would we have instilled public confidence in our work if we had departed from an impartial, considered analysis of the evidence.
4. It did mean that we worked hard to deliver not only a balanced and proportionate outcome but a sustained and quality engagement with those directly affected. We sought to do this sensitively and with understanding, recognising that their willingness to participate would of itself bring some therapeutic benefit, a part of the healing process, to those whose voices had yet to be heard.
5. **Second**, that we were, and were perceived to be, truly independent. Although funded by the Department of Health and Social Care (DHSC), our processes and our findings were ours and ours alone to make. We were determined to probe wherever the evidence led us. We would speak without fear or favour. To emphasise this we

⁵⁴¹ The Panel of the Independent Medicines and Medical Devices Safety Review had the following members: Baroness Julia Cumberlege CBE DL (Chair), Professor Sir Cyril Chantler GBE (vice Chair), Simon Whale – panel member with specific responsibility for stakeholder engagement and communications. Information about the Panel’s members and their interests was made available on the Review’s website at www.immdsreview.org.uk

incorporated the word ‘Independent’ in our title. None of the three members of the Panel (the ‘decision takers’) have an interest in the pharmaceutical industry or in the regulatory bodies.⁵⁴² None of the senior members of the Review’s Secretariat were seconded from our sponsor Department. Our modest offices were located in non Government, non NHS premises at King’s College London.

6. **Third**, that the Review would be open and transparent. The families, the patient groups and the public would know what the Review was doing at every stage because we would tell them. We set up our own website where we posted information about the Review and its processes, as well as regular updates and a Chair’s blog. We published the evidence sought and received (see below). We also communicated regularly through Twitter. Our aim was maximum possible disclosure and a commitment to transparency. We operated an open door policy, accessible to anyone who wanted to talk to us about any of the three interventions with which the Review was concerned or any other matters that had a bearing on our Terms of Reference (ToR).
7. Similarly, we expected that those from whom we needed to hear in order to deliver our ToR would be open and transparent with us and would provide such material and documentary evidence as we requested. On occasion it would be necessary, however, to redact information which related to confidentiality or which included personal information (this was in line with the Review’s policy).⁵⁴³ Redaction would also be necessary if information was otherwise considered unsuitable for publication for a good substantial reason (which would include legal professional privilege). To that end, the Review first wrote in May 2018 to stakeholders, the DHSC, the regulators and manufacturers, an ‘expectations’ letter asking them to ensure all necessary records of evidential value would be preserved and offered to the Review on request.
8. **Fourth**, there would be no piecemeal disclosure of our findings and recommendations and there would be no interim report. Equally, however, this Review would not itself become part of the problem and fail to ‘*listen, hear and act with speed and proportionality*’ when it became aware of the risk of serious and ongoing harm. In July 2018, NHS England and the DHSC acted on our advice and agreed to the immediate cessation or ‘pause’ in the use of surgical mesh for

⁵⁴² All three Panel members receive a stipend from NHSE for their work on delivering ‘Better Births’ to improve maternity services in England. In addition, the Review’s Vice Chair, Professor Sir Cyril Chantler, is a non-executive Director of PHIN (the Private Healthcare Information Network). This is an independent not-for-profit organisation that publishes trustworthy comprehensive data to help patients make informed treatment choices. It is mandated by the Competition and Mergers Authority (CMA) but paid for by a levy on the cost of private care. Sir Cyril held that position throughout the Review.

⁵⁴³ See IMMDS Review Anonymity and Redaction policy <https://immdsreview.org.uk/downloads/Anonymity-and-Redaction-Framework.pdf>

the treatment of stress urinary incontinence until certain conditions had been met. This was one example of the Review putting this principle into practice and being forthright and timely in its early recommendation (see Chapter 5). There are others which we refer to throughout our report.

Patient engagement

9. Our earliest meetings were with the patient groups who came forward and made themselves known to us as representing and supporting those directly affected by our three interventions. Not all the groups were known to us at first, with others making contact over the life of the Review as news of our work spread.⁵⁴⁴ The purpose of these and subsequent meetings was for us to understand the issues of concern for them, the pressures and challenges they and their families faced in their daily lives and what had driven them to campaign for so long.
10. We have nothing but praise for these patient groups and their willingness to go the extra mile to share their knowledge and understanding and work co-operatively with us throughout the Review. They never wavered in their efforts to assist us in our work. That there were so many groups - particularly in relation to pelvic mesh, less so for valproate – did not impede the way we worked.⁵⁴⁵ These groups were established and developed in response to the perceived needs of those they set out to support. They adopted different approaches to further their aims – whether as a Facebook messaging and information sharing service, as media or political campaigners and as advice and support givers. We respected the differences between them and worked with them collectively or individually as best suited them. We did not at any time follow or otherwise engage in discussions between, or observations about, the patient groups being played out on social media. To do so would have irreparably damaged our impartiality.
11. In parallel with these early meetings with the patient groups we held a series of preliminary meetings with clinicians and others to help support the Panel's own learning and so better understand the medical conditions of those affected.⁵⁴⁶ Towards the end of the Review, and after we had finished taking evidence, we held further informal meetings to test the limitations of what was practically doable so that we could shape our recommendations and deliver a report that could be implemented. Those meetings are listed in Appendix 5.

⁵⁴⁴ See Appendix 5 for a full listing of the patient groups that we engaged with over the course of our work.

⁵⁴⁵ There is only one patient support group for Primodos, the Association of Children Damaged by Hormone Pregnancy Tests (ACDHPT).

⁵⁴⁶ Although the Vice-Chair has a distinguished medical background it is in an unrelated specialism.

12. We also wanted to hear early on from the chairs of the three All-Party Parliamentary Groups (APPGs) to understand their issues of concern and the progress they had made to address these through the political channels.⁵⁴⁷
13. This dialogue with politicians and patient groups continued throughout the Review in a variety of ways – through regular exchanges of correspondence, through the patient engagement events, the Call for Evidence and oral hearings, the patient group feedback events and finally as part of the Review’s report launch. It helped shape (but not determine) our thinking at every stage, starting with our ToR, provided invaluable insight and knowledge sharing and offered a fount of creative and practical problem solving ideas. Given the numbers of patient groups involved, this way of working and our continuous open door engagement allowed us to tap into their considerable breadth and depth of experience.
14. Finally, we produced a poster for display in GP practices and community pharmacies to raise awareness of the Review’s work and to give contact details to those who might wish to get in touch with or provide us with evidence. We would like to thank NHS England and its Clinical Commissioning Groups for their help in bringing the poster to the attention of our target audience and making copies of the poster readily available.

Developing our Terms of Reference

15. The building blocks for our TOR were laid down by the Secretary of State in his announcement of the Review.
 - Firstly, to assess the robustness and speed of the processes followed by the relevant authorities and clinical bodies, to ensure that appropriate processes were followed when safety concerns were raised;
 - secondly, whether the regulators and NHS bodies did enough to engage with those affected to ensure their concerns were escalated and acted upon;
 - thirdly, whether there has been sufficient coordination between the relevant bodies and the groups raising concerns; and
 - fourthly, whether we need an independent system to decide what further action may be required either in these cases or in the future in order to

⁵⁴⁷ All Party Parliamentary Group on HPTs, All Party Parliamentary Group for Valproate and other Anti-Epileptic Drugs, All Party Parliamentary Group on Surgical Mesh.

ensure that justice is done and to maintain public confidence that such decisions have been taken fairly.

16. Extensive engagement with the patient groups and the APPGs helped us to shape, refine and clarify our draft ToR for circulation to an extensive group of stakeholders. Those who commented on the draft ToR or who sought further clarification including relevant manufacturers, some Royal Colleges and professional bodies, some regulatory bodies and some of the patient groups, are also listed in Appendix 5.
17. Our final ToR (see Appendix 1) were published on our website in September 2018. This was followed by the publication of a suite of documents describing the Review's processes to ensure a) that sensitive personal information provided to the Review would be handled in a safe and ethical way and in compliance with the Data Protection Act of 2018 and b) we were as far as possible consistent in our approach and could be held to account accordingly.⁵⁴⁸ In addition we registered with the Information Commissioner's Office as a data controller.⁵⁴⁹

Patient engagement events

18. Hearing from the patient groups heralded the start of our listening and learning. We gave priority to meeting with patients and families to hear their stories first hand. We worked with the patient groups to determine where across the country we should travel. We met patients and their families wherever they felt most comfortable – whether it was a local community hall, a family centre for the disabled or a hotel conference suite.
19. Altogether we held 16 drop in events and met over 700 affected individuals and families. The informality of these meetings did nothing to lessen their highly charged and emotional content. For many they offered an opportunity to talk with one another in small groups and to us about their experiences and the impact of their intervention on them and their families. Although each story was unique, there were a number of common and compelling themes which we describe throughout this report. Some spoke out for the very first time, for some it was an opportunity to meet others and know they were not suffering alone. Many reported that finally someone was prepared to listen to them.

⁵⁴⁸ Our process documents included:

- The Review's process protocol
- How we handle the information you provide to the Review – Data protection and privacy
- Anonymity and Redaction Framework
- Consent to use your Personal Information for the Independent Medicines and Medical Devices Safety Review.

⁵⁴⁹ The Review's ICO reference number is ZA442316.

20. We heard from patients by letter and by email, each wanting to share their personal testimony and describe their experiences. Altogether by this means we heard from over 500 people affected by these interventions. Although we agreed not to publish these or the stories that we heard at our patient engagement events, they provided the context against which to probe and test the evidence submitted by stakeholders including manufacturers, clinicians, professional bodies, health care providers, the NHS arms-length bodies and the DHSC. Patient stories and testimonies ensured that our key lines of enquiry were properly grounded in their experience.

Counselling service

21. In so many cases, sharing personal testimonies, stories and experiences involved those affected disclosing intimate details about their bodies, about their lives and about their personal relationships. Their sadness, anger, pain and frustration at what had happened to them was very much in evidence. We recognised that the act of sharing this information took great courage and likely caused distress. Our aim was to ensure that those who wanted to engage with us felt emotionally supported to do so. To that end we funded a telephone counselling service, freely available to all who might need it, offering up to two one hour counselling sessions delivered by trained counsellors. Where more ongoing support was called for, the counsellors could, and did, signpost and assist users to access local mainstream mental health support services.⁵⁵⁰
22. In total over 119 people availed themselves of this service⁵⁵¹. The overwhelming majority had been affected by their experiences with pelvic mesh.
23. Where possible we tapped into local health services and sought their assistance in providing a counsellor to attend our patient engagement drop in events. It is a measure of the pressure these services face that we achieved this at only two of our sessions – one in Manchester and one in Leeds.⁵⁵² This was a great pity as the presence of a counsellor at these two events was particularly well received.

Call for Evidence

24. Our Call for Evidence, which opened on 18th September 2018 and closed on 24th October 2018, allowed any person, body or organisation to submit evidence

⁵⁵⁰ The counselling service was provided by Citizen Coaching C.I.C.

⁵⁵¹ This is the figure to end January 2020.

⁵⁵² We are grateful to Greater Manchester Mental Health NHS Trust for their support and assistance at these two events.

and upload any documents relevant to our ToR that they wished to share with the Review.⁵⁵³ We accepted a number of submissions which were received after the closing date.

25. In addition to the general Call for Evidence we sent out tailored questionnaires to a wide range of individuals and organisations. Each invited a submission and outlined the questions we hoped the recipients would answer in addition to any other information they wished to include. The full list of those sent questionnaires included:

- pelvic mesh manufacturers
- valproate manufacturers
- manufacturers of hormone pregnancy tests (HPTs) or their legacy companies
- trade associations for medical devices companies and pharmaceutical companies
- a wide range of NHS bodies and organisations
- regulatory bodies including the Medicines and Healthcare products Regulatory Agency, Care Quality Commission, General Medical Council and General Pharmaceutical Council
- NHS arms-length bodies including NHS England and NHS Improvement (joined during the course of the Review), and the National Institute for Health and Care Excellence
- NHS and independent health care providers
- the Department of Health and Social Care
- relevant Royal Colleges and professional clinical associations
- established Registries and database holders
- individual clinicians

⁵⁵³ The Call for Evidence deadline did not apply to patients and families affected by any of our three interventions. They continued to share their personal testimonies and submit any other additional and relevant information throughout the life of the Review. Others who sought an extension to the deadline were considered on a case by case basis. We offered the option of an online template as an alternative to submitting evidence by email or post. Each submission was entered into our data management system, coded with a unique identifier number and where personal identifiable information was disclosed, the appropriate consent permissions for the Review to store and analyse that information were sought.

- private health care providers and their trade bodies
 - administrators of existing compensation redress schemes.
26. Other than the patient groups, each person or organisation who responded to our Call for Evidence was asked to complete a conflict of interest statement which was published alongside the evidence they submitted.⁵⁵⁴

Processing the Evidence Received

27. Those who provided written responses during or after the Call for Evidence period are listed in Appendix 5. Evidence came in a range of different formats: paper documents, newspaper articles, medical and other paper records, electronic documents, photographs and videos. Each was catalogued and checked against our data handling and anonymity and redaction frameworks.
28. These frameworks allowed for redactions to be made on the grounds of personal identifiable data, relevance to the Review's ToR, and information given in confidence or otherwise deemed to be commercially sensitive. The Review was also bound by the rules of legal professional privilege, where this was put forward as a factor.
29. Once checked against our own processes the evidence submitted and, where relevant, the tailored questions posed, were uploaded on our website in line with our principle of maximum disclosure. When possible, where submissions referred to material already in the public domain we posted electronic links to that material.
30. Although not a Review backed by statute, and therefore without powers to enforce disclosure, we received a huge amount of evidence from a wide range of stakeholders – many of whom contributed to our work throughout the life of the Review and we remain appreciative of that contribution. Others chose not to, despite repeated reminders.⁵⁵⁵
31. As an addendum to the general Call for Evidence, we sought written responses to targeted questions from 26 mesh centres listed on the British Society of Urogynaecology's (BSUG) website. In total we received 17 responses. These revealed a far from uniform approach to gathering the data we had requested,

⁵⁵⁴ All those other than the patient groups were asked to complete the following declaration: 'Do you have any commercial/financial/legal connection or interest in the pharmaceutical and medical devices industry sector or any other body or organisation of interest to the Review?'

⁵⁵⁵ Those who did not respond to our Call for Evidence or who acknowledged our request but did not submit any written evidence in response are listed in Appendix 5. Some, however, subsequently attended an oral hearing session.

making our analysis and evaluation that much harder to complete. Indeed, we were struck by the huge variability in the surgical and treatment data these units were able to provide covering the 10 year period 2008-2018. We were also struck by how often coding issues were cited as the reasons for inaccurate or incomplete data retrieval especially for mesh removals, the poor recording of Yellow Card adverse event reports and the variability in reporting of mesh procedures onto any of the recognised clinical associations' databases.

32. We agreed that both the targeted questions and a summary report of the Trust returns would be published on our website and that these would be anonymised in order to encourage the mesh centres to be open in their responses.

Oral hearings

33. The next phase of our work was the oral hearings. In total we held 78 oral hearing sessions between November 2018 and the end of May 2019. Not all those invited to attend agreed to do so and we comment on this later. Those who did are listed in Appendix 5. Although not open to the public, all sessions were filmed and once edited in line with the Review's frameworks (discussed in paragraph 17), were posted on the Review's website.
34. In line with our 'families first' approach, we invited the patient groups to appear before anyone else. And we gave them an opportunity to return for a second oral hearing at the very end enabling them to share with us, should they choose, their reflections on what we had heard from others who were invited to appear before us. On this basis, patient groups would have the first and last say in our oral hearings process.
35. The purpose of these hearings was twofold:
 - first, to give stakeholders an opportunity to share with the Review Panel the information they believed we needed to know to deliver the Review's ToR ;
 - second, to give the Review Panel the opportunity to probe the evidence received, ask additional questions and seek further clarification as necessary.
36. For the patient groups they served a further purpose. We invited them to bring someone directly affected by one of the three interventions, who would be willing to share the impact on their lives and that of their family by what had happened to them, and to describe their concerns and hopes for the future. Our aim was to give public voice to all the written personal testimonies we had received during the

Review and the stories we had heard on our patient engagement visits around the country. Those who came spoke with extraordinary dignity and eloquence. We can only admire their bravery and courage.

37. Patient groups were followed by clinical and scientific experts both of the patient groups' choosing and our own, followed by manufacturers, health professionals, Royal Colleges and public and private health care providers, other public bodies including the regulators, NHS partner agencies and the DHSC. The three APPGs that had worked tirelessly to push HPTs, valproate and other anti-epileptic drugs and pelvic mesh on to the political agenda also came to give evidence, prior to the patient groups' final say hearings in May 2019.
38. Baroness Cumberlege chaired every oral hearing session and, with one exception all three members of the Review Panel, attended and participated fully in the exchange of questions and answers at each of those hearings. The Panel were supported by the Review's lead researcher, Dr Sonia Macleod, and the Review Secretary Dr Valerie Brasse.⁵⁵⁶ All the oral hearing sessions were held in central London. Where substantive criticisms of a person or organisation were made during a hearing we considered, in line with our processes, giving that person or organisation the opportunity of a written Right of Reply. These responses were then published on the website and linked to the relevant oral session. We are grateful to all those who contributed to this lengthy and protracted process and for their patience in seeing it through to the end.

Patient groups – stakeholder feedback events

39. Critical to the analysis of the evidence we received was an understanding of the significant events during the lifetime of the three interventions. Given the time spans we were investigating – over 40 years for both Primodos and Valproate and more than 20 years for pelvic mesh – this was to prove a highly complex exercise. The resulting draft timeline documents, each over a hundred pages, drew on seminal research papers, reported or known actions and decisions taken by regulators, manufacturers, professional associations as well as exchanges of correspondence between them. Taken together this information helped to chart the changes in the regulatory frameworks and in contemporary thinking and knowledge over time. They helped answer the questions who should have known what and when, and how as a result should those with a responsibility for patient safety have acted.

⁵⁵⁶ The Vice-Chair was unable to attend the sessions on 16th April 2019 because of a diary clash with another key Review related meeting.

40. We were helped hugely in this task by the patient groups, many of whom had pulled together their own timelines of significant events for us to build on. In September 2019 we invited the patient groups back to hear whether they felt there were any significant omissions in our work and, based on these draft timelines, to identify the missed opportunities as they saw them.
41. Their contributions in these meetings were spirited, well informed and of great value. We know that some patient groups will be disappointed that the Review did not accommodate every addition suggested. We were, however, mindful of the need for these timelines to maintain their focus on key events, to include only that material that fell within our ToR, to establish provenance for a study or document, if this was within doubt, and to respect legal professional privilege where this might apply.
42. We acknowledge that we originally stated to attendees we intended to publish the audio transcripts of these meetings. However, we came to realise this would not be appropriate. This is because the transcripts contain details which would require extensive redaction. This, in turn, would distort the overall meaning or context of what was said. However, the Panel wishes to emphasise that it has taken into account everything which was said at these meetings (the purpose of which was to consider the timelines and prepare them for publication).

How Organisations assisted the Review in its work

43. We pay tribute to the dedication and effort put in by the patient groups and the APPGs who supported them in assisting us with our work. Where we have asked for extra evidence they have provided it, calling on their members as and when they felt this would add to the quality of their input. They have generously shared with us their extensive knowledge, research and analysis.
44. Most other bodies and organisations we have approached, including a number of the DHSC's arm-length bodies, have understood the significance of this Review in seeking to comment both on the events of the past and the lessons to be learned for the future and have co-operated with us from the outset. Others chose to engage on their own terms.

The Department of Health and Social Care

45. In response to our ‘expectations’ letter of the 1st May 2018,⁵⁵⁷ the Permanent Secretary, Sir Christopher Wormald, wrote on 17th May 2018 as follows:

*‘...the Department will of course preserve all necessary records as well as be open and transparent in offering evidence of value to the Review. We anticipate that some information may need to be passed to you in confidence, for example where individuals have given personal medical histories. In this case we will need to agree on public reporting of this information, taking into account the Department’s responsibilities under GDPR. On other occasions the volume of evidence may be an issue for you. In all cases my officials will be happy to work with the Review team to ensure that you have the appropriate evidence’...*⁵⁵⁸

46. We were grateful for these assurances. The tailored questions put to the DHSC were emailed to the Permanent Secretary’s Office on 19th September 2018.
47. Baroness Cumberlege wrote to the Permanent Secretary on 23rd January 2019. In this letter she reiterated her appreciation of his earlier assurances and invited the Permanent Secretary to attend an oral hearing later in the year.
48. On 19th February 2019, the Permanent Secretary responded. He raised a concern that as commissioner of the Review the Department must be seen to maintain clear impartiality as to how the Review goes about its work and stated:

*‘we must therefore avoid any appearance of influencing your work or commenting on policy ahead of your recommendations. We are particularly keen to ensure that there is no suggestion of Departmental influence or of our pre-judging the outcome, particularly when you have made your conclusions. It is important for the Department to use your conclusions as the starting point for further policy thinking - and for that to be clear to the public and stakeholders.’*⁵⁵⁹

He repeated his keenness for the Department to assist the Review and stated that many of the questions we had asked fell within the remit of ‘our health system partners’ who are in the best position to answer them.

⁵⁵⁷ See paragraph 7.

⁵⁵⁸ Letter to Baroness Cumberlege from Sir Chris Wormald, Permanent Secretary, DHSC, dated 17th May 2018 – see DHSC written evidence to the Review.

⁵⁵⁹ Letter from Sir Christopher Wormald, Permanent Secretary DHSC to Baroness Cumberlege of 19th February 2019 – see DHSC written evidence to the Review

49. A document setting out the ‘key policy/Departmental position’, in effect the Department’s written evidence submission, was attached to the letter. In addition, we were provided with access to the Department’s correspondence database (searchable only since 2008) for us to conduct our own search (with the support of the Department’s records team) in order to gauge the level of concerns that had been raised with the Department.

50. As we did not undertake a rigorous investigation of the database using every possible linked search term we cannot vouch for the accuracy of the numbers we found. Nonetheless, they do appear low when considered against the correspondence received by this Review across all three interventions, since its start in February 2018, much of it dealing with historic events and patient experiences. In concluding his letter of 19th February 2019, the Permanent Secretary stated that the Department had no ‘settled policy’ on the issues the Review was looking into – indeed that is why the Review had been set up.

51. The position in which the Department found itself perhaps demonstrates a fundamental difficulty. In other words, the sponsoring Department here is the same Department which may be responsible for any policy decisions arising out of matters identified by the Review. Yet, as an independent Review our findings and recommendations are ours and ours alone to determine and the evidence provided by the Department, or indeed any other stakeholder, should have no bearing on that. We consider this issue later in this chapter (paragraphs 73 - 74).

52. On 8th March 2019 the Permanent Secretary wrote that he accepted the invitation to attend a Review oral hearing acknowledging that *‘it would be helpful for you to hear from us regarding the history of events’*.^{560,561}

53. We are grateful to the Permanent Secretary, the former Chief Medical Officer, Dame Sally Davies, and William Vineall, Director of Acute Care and Quality Policy for attending a Review oral hearing on 2nd May 2019. We also appreciated the Department’s assistance in facilitating access to all the archived files requested by the Secretariat. These included Department of Health files that had been closed for 100 years relating to the Committee on the Safety of Medicines and minutes of meetings of the Sub-committee on Vaccination and Immunisation.⁵⁶² These ‘closed’ files had been identified by one of the patient groups as being potentially relevant to our work. On inspection by the Secretary of the Review and members of the investigative team this did not prove to be the case.

54. It is, however, to be noted that we were unable to locate any of the minutes of the Standing Joint Committee on the Classification of Proprietary Preparations (known as ‘the MacGregor’ Committee) for the years 1969 until it was wound up in 1971. The role of the Committee was to help doctors decide which preparations should

be used in treatment and to identify those preparations that required special justification for use. Committee minutes from 1969 might have contained useful information and a record of the discussion leading up to its decision to request the withdrawal of the indication for pregnancy of HPTs from the manufacturers in 1970. These minutes must have existed, and yet the Department was unable to assist in determining their whereabouts or to confirm whether or not they had been destroyed.

The Manufacturers

55. Critical to our understanding of past events has been the activity of the manufacturers in relation to each of our three interventions, their pre and post marketing surveillance obligations and their commercial, legal and ethical responsibilities to seek and act on adverse event information.
56. At each key stage in our Review we have engaged with the manufacturers and offered opportunities to contribute to our work. As well as understanding the events of the past, we also wished to explore with them how in future the pharmaceutical industry can help shape a healthcare system that better listens and responds to patient safety concerns. The manufacturers we engaged with are world leaders in their field and we hoped they would wish to take part in such a conversation. All three of the leading manufacturers Bayer, Sanofi and Ethicon (Johnson & Johnson) engaged with us throughout the Review. Only Sanofi, the manufacturer of Epilim (valproate as marketed in the UK), agreed to attend an oral hearing.

HPTs

57. Primodos, the leading HPT in the UK, was manufactured by Schering in Germany. It was withdrawn from the UK market by Schering in 1978 and the Schering company was itself acquired by Bayer plc in 2006 (see Chapter 3). In response to our communications Bayer both commented on our draft ToR, and responded to our Call for Evidence. Their written submission is on our website.
58. In their letter of 13 December 2018,⁵⁶³ Bayer commented *‘We should emphasize that dealing with these questions for any company would be very difficult, given that they largely address events relating to the marketing of a product over 40 years ago. In our case the difficulty is accentuated as Bayer companies never marketed Primodos and their involvement only arises through the acquisition of Schering in*

⁵⁶³ Letter from Mark Wilkinson, Head of Legal and Compliance, Bayer plc to the Review Secretary dated 13th December 2018. See written evidence.

2006. We, therefore, have no first-hand knowledge of the history of the matter and the actions of Schering. The documents on this product held by Schering Chemicals in their old premises were long since destroyed. If the key scientific and medical staff involved in the relevant period at either Schering Chemicals or its parent company are still alive (which we doubt) they are certainly not employees of Bayer plc today’.

59. Bayer went on to explain that they were able to provide fairly detailed answers to the Review’s questions because *‘the UK lawyers for Schering Chemicals at the time of the litigation maintained in their archives a selection of key regulatory documents relating to the history of marketing in the UK’...* and further stated that they were *‘not in a position to confirm the completeness or accuracy of the information provided...’.*

Bayer concluded by saying that against this background, *‘there is nobody at Bayer plc who could usefully contribute anything on the subject matter of your inquiry, we respectfully decline your offer to attend the oral hearing planned for next year’.*

60. The Head of Legal Affairs at Bayer’s UK office subsequently commented *inter alia* in a letter dated 28 January 2019,⁵⁶⁴ that, *‘in the circumstances, it does not seem appropriate that Bayer gets involved in oral hearings on these issues and is content to leave recommendations concerning the current healthcare system to the careful judgment of your Review Team’.* Bayer wanted to continue to co-operate with the Review, and agreed to respond in writing to any further written questions. That further exchange of written questions and answers continued throughout the Review. This was much appreciated.
61. Baroness Cumberlege wrote to the Chief Executive of Bayer, Herr Werner Baumann, on 1st February 2019. This was to let him know the importance she attached to Bayer’s presence at an oral hearing, and asking that he reconsiders the company’s position so that we could have an open discussion with senior representatives not only about the past but about lessons to be learned for the future.
62. On 22nd June 2019 we received a response from Herr Oliver Renner, Head Pharmaceuticals Communication and Health Policy, writing on behalf of the Chief Executive of Bayer.⁵⁶⁵ In a detailed email, Herr Renner explained that the delay in replying was due to the fact that they firstly wanted the Review to receive their responses to the questions which the Review had put to them. He went on to say that: *‘...The key scientists and other personnel at Schering in the 1960s and 1970s and involved in these matters are not employed by Bayer and most are probably*

⁵⁶⁴ Letter from Mark Wilkinson, Head of Legal and Compliance, Bayer plc to the Review Secretary, dated 28th January 2019. See written evidence.

⁵⁶⁵ Email from Oliver Renner to Lady Cumberlege, dated 22nd June 2019. See written evidence.

deceased. In the circumstances, nobody at Bayer is able to speak knowledgeably about the issues you have raised and, therefore, the face-to-face discussions you seek could not make any useful contribution to your examination of the history of this matter’.

63. He further explained that *‘...the entire regulatory system relating to research and marketing of medicinal products has substantially changed and public health and patient interests have been central to those changes. Bayer, therefore, does not believe that any comparison between the system in the 1950-70s and that which prevails today would be useful and, in any event, Bayer is in no better position to address those changes than any other pharmaceutical company.*
64. He concluded by saying that he *‘believed that there would be no benefit to be derived for your Review from a Bayer employee participating in an oral hearing to discuss matters with which he or she had no involvement and has no personal knowledge’.* In this email, Bayer stated that they did their best to answer factual questions concerning Primodos (where information was available to them from historical papers) and they also considered that they co-operated fully with the Review. It is our view, nevertheless, that it would have been helpful if they had attended the oral hearing.
65. During the course of our work, it was also necessary for us to seek the appropriate permission from Bayer in order to rely on certain documents. We were able to partly resolve this issue and we draw attention to the statements which both Bayer and the Review have made in this respect.

Bayer statement concerning Landesarchiv documents

During the course of the Review, the Review Team has viewed documents which derive from files of internal documents belonging to Schering AG that, in the late 1970s, were seized by the relevant federal authorities in Germany as part of a review which they conducted relating to hormone pregnancy tests.

These documents have since been stored at the Landesarchiv Berlin. They date principally from a period after sales of Primodos and other HPTs ended in the UK. The documents were subsequently made available to the MHRA for consideration by an Expert Working Group of the UK's Commission on Human Medicines which was established in October 2015 in order to conduct a review to ascertain whether the totality of the available data, on balance, support a casual association between use of an HPT by the mother and adverse pregnancy outcomes.

These documents were not made available by Schering/Bayer and Bayer has drawn to the Review's attention the fact that it has not waived any rights it has in the UK or elsewhere relating to confidentiality and privilege which attach to these documents.

IMMDS Review statement concerning Landesarchiv documents.

The Review sought permission from Bayer to rely on these documents and in this respect, we would draw attention to a statement which the Review has included in its report (here), and on the website and timeline at Bayer's request.

It is important to note, that for legal reasons asserted by Bayer, it has not been possible for the Review to provide the detail of certain documents in the report. This has meant that the Review has been limited to the extent in which it could set out the text or contents of these documents in its report, although it has read them and relied on them in coming to its findings. Additionally, Bayer has asked the Review not to publish or to provide links to the documents in question.

Pelvic mesh

66. We sent out our Call for Evidence to a number of mesh companies and received written responses from the following (all are posted on our website):

- Boston Scientific
- Ethicon (Johnson & Johnson)

- FEG Textiltechnik
- Medtronic.

67. Of these, we invited only Ethicon (as one of the largest suppliers of pelvic mesh) and FEG TextilTechnik of Germany (the only manufacturers of Polyvinylidene fluoride (PVDF) mesh as opposed to polypropylene mesh) to an oral hearing. FEG TextilTechnik attended on 23rd January 2019 and continued to work with us by answering follow up questions in writing.
68. Ethicon provided a substantive response to our written Call for Evidence questions. However, they declined to attend an oral hearing. As with Bayer, Baroness Cumberlege wrote to the Chief Executive and Chairman of the Board, Alex Gorsky on 1st February 2019 requesting he reconsiders the company's position and asking the company to send senior representatives who could engage with the Panel in an open conversation about the past and about the lessons to be learned for the future.
69. On the 5th April 2019 Mr Vladimir Makatsaria, the Company Group Chairman, wrote to say that Ethicon:

'empathises with all women who suffer with debilitating pelvic conditions, especially those who have experienced treatment complications with or without the use of a pelvic mesh. At the same time it is noteworthy that millions of women worldwide with pelvic mesh have seen an improvement in their day to day lives'.⁵⁶⁶

70. Mr Makatsaria went on to say that they *'...wish to continue to assist the enquiry being undertaken by your Review Team...'* and that the *'detailed written responses and supporting documentation provided by Ethicon to the Review Team...were the result of considerable effort and collaboration on the part of a team of specialists in different roles at Ethicon, both in the EU and USA, to ensure that we were fully able to address the in-depth questions and requests presented by your Team'*.

He also stated that '...because the questions may cover a broad range of topics that would fall under the remit of several different sections, individuals, and specialities within Ethicon, representatives would be able to speak only partially to some of the questions. We remain concerned that this discussion would not provide your Review Team with properly informed, complete or in-depth responses.

⁵⁶⁶ Letter from Mr Vladimir Makatsaria, Ethicon Company Group Chairman to Baroness Cumberlege on 5th April 2019.

Accordingly, after careful consideration, our position remains that in order to provide the Review Team with the level of detail and information that it reasonably and properly requires, we invite the Review Team to provide us with the additional questions they may wish to ask and we will address them carefully and respond in writing as soon as possible’.

71. Ethicon have continued throughout the Review to answer our follow up questions in writing promptly and in detail. Both the questions and Ethicon’s responses have been published on our website and we greatly appreciate the company’s willingness to contribute in this way to our work. Nevertheless, as with Bayer, the Review considers it would have been helpful if Ethicon had attended the oral hearing.

Working with our sponsor Department

72. Finally, we comment on our relationship with our sponsor Department. Although established as an independent, non-statutory Review we were funded by the DHSC who, as is customary, acted as our sponsor Department. As others have commented before us,⁵⁶⁷ and as our own experience demonstrates, this is an unsatisfactory arrangement conceptually and was to prove on a practical day to day level frustrating to us.
73. First, there is the inevitable perception that a review funded by the DHSC could not properly investigate its own conduct, nor the conduct of its partner agencies, with the necessary independent rigour. Yet, it is these very same agencies and ultimately the Department whose decisions taken (or not) and whose positions adopted over a very lengthy history, in the case of all our three interventions, that were necessarily the subject of our inquiries.
74. In his correspondence with the Review, and in his oral evidence Sir Christopher Wormald, Permanent Secretary at DHSC, recognised this conflict explicitly. Similarly the decision taken by the Government to place the sponsorship of the statutory Inquiries of Grenfell Tower and Infected Blood into the Cabinet office, rather than traditionally in the department with the closest policy links to the issues under investigation, appears to be in our view a recognition of the same concern.
75. Secondly, as the holders of the Review’s purse strings the Department could and did seek to exercise control over how the money initially agreed by the Secretary of State for the purpose of the Review was disbursed during the Review’s lifetime. Although the Review acted independently and determined its own programme of work, and the resources needed to support that work, the experience of having

⁵⁶⁷ Sir Robert Francis, QC (Mid Staffs Inquiry) House of Lords hearing, 30th October 2013.

to justify in advance a business case for each element of spend within that agreed budget proved both time consuming and frustrating. This is not to find fault with individual civil servants tasked with the proper scrutiny of public spending. It arises from a set of budgetary processes that do not reflect the reality of running a hugely complex Review – a Review that may, as in our case, need to be agile in its response to emerging circumstances and require some flexibility of approach whilst still ensuring overall budget constraints are met. It also highlights the lack of a central repository of knowledge and capacity within the Department – or indeed elsewhere in Government – that can ably support a review to deal with the efficient procurement of staff, accommodation, IT and legal support and final decommissioning – practical challenges that each new Inquiry or Review faces afresh every time.

76. It has been suggested elsewhere that an independent office established to support Inquiries and Reviews is the only sensible approach to follow.⁵⁶⁸ Such an office, properly resourced and accountable to an elected committee of Parliament, would both resolve the inherent tensions in the current Whitehall practice of sponsoring Reviews and could support new Reviews in the very practical start up challenges they face. It could also provide the mechanism to assist in the monitoring and implementation of each Review or Inquiry's recommendations and so ensure they represented value for money. We agree.

Appendix 5: The Review in facts and figures

1. Patient groups that interacted with the Review
2. Responses to Terms of Reference
3. Patient engagement events
4. Responses to our Call for Evidence
5. Oral hearings
6. Review meetings
7. Independent Medicines and Medical Devices Safety Review

1. Patient groups that interacted with the Review

Through the course of its work the Review interacted with the following patient groups:

PELVIC MESH
Action for Mesh Injured Patients
Mashed up by Mesh
Mesh Awareness Wales
Mesh Ireland
Mesh UK Charitable Trust
Meshies United Group UK
Rectopexy Support Group
Scottish Mesh Survivors
Sling the Mesh
The Voices Today on Messed Up Mesh (TVT MUM)
Welsh Mesh Survivors Support Group

HORMONE PREGNANCY TESTS
Association for Children Damaged by Hormone Pregnancy Tests (ACDHPT)
SODIUM VALPROATE
FACSaware
Independent Fetal Anti-Convulsant Trust (INFAC) and Fetal Anti-Convulsant Syndrome Association (FACSA)
Organisation for Anti-Convulsant Syndrome (OACS)
Organisation for Anti-Convulsant Syndrome (OACS) Ireland
Valproate Victims
Young People Affected by Valproate

2. Responses to Terms of Reference

The Review received 17 responses in total to the Draft Terms of Reference. The full list of organisations that responded is as follows:

Royal Colleges (3)
Royal College of Obstetricians and Gynaecologists (RCOG)/British Society of Urogynaecology (BSUG) (joint response)
British Association of Urological Surgeons Limited (BAUS) – Section of Female, Neurological and Urodynamic Urology
Royal College of General Practitioners (RCGP)
Regulatory bodies (3)
Medicines and Healthcare products Regulatory Agency (MHRA)
National Institute for Health and Care Excellence (NICE)
Devices Expert Advisory Committee (DEAC)
Manufacturers (4)
Ethicon/Johnson & Johnson
FEG Textiltechnik
Sanofi
Bayer
Political Stakeholders (1)
Scottish Government (Medicines Policy)
Patient Groups (6)
Association for Children Damaged by Hormone Pregnancy Tests (ACDHPT)
FACSaware
Independent Fetal Anti-Convulsant Trust (INFAC) and Fetal Anti-Convulsant Syndrome Association (FACSA)
Mesh UK
Organisation for Anti-Convulsant Syndrome via Leigh Day
Sling the Mesh

3. Patient engagement events

Locations and Number of Attendees – ALL

LOCALITY OF EVENT	DATE OF EVENT	NUMBERS AFFECTED BY HPTs*	NUMBERS AFFECTED BY SODIUM VALPROATE	NUMBERS AFFECTED BY PELVIC MESH	TOTAL ATTENDEES
CHICHESTER	26 th June 2018		13		13
LEICESTER	29 th June 2018		6		6
LONDON	3 rd July 2018		11	20	31
MANCHESTER	11 th & 12 th July 2018	59	13	27	99
SOUTHAMPTON	14 th August 2018	36		51	87
HULL	30 th August 2018		14	28	42
LEEDS	12 th September 2018	22	9	38	69
OXFORD	17 th September 2018			44	44
CAMBRIDGE	15 th October 2018		3	17	20
CARDIFF	30 th October 2018		10	30	40
NEWCASTLE	12 th November 2018			30	30
GLASGOW	13 th November 2018		4	72	76
	17 th April 2019			58	58
BELFAST	6 th December 2018		9	48	57
EXETER	13 th December 2018		9	35	44
BRISTOL	30 th January 2019		3	19	22
TOTAL		117	104	517	738

* The decision to hold three meetings for those affected by hormone pregnancy tests (HPTs) was that of the *Association for Children Damaged by Hormone Pregnancy Tests (ACDHPT)*

Locations and Number of Attendees – England and Devolved Authorities

	FAMILIES AFFECTED BY HPTs	FAMILIES AFFECTED BY SODIUM VALPROATE	WOMEN AFFECTED BY PELVIC MESH	NUMBER TOTAL ATTENDEES	PERCENTAGE OF TOTAL ATTENDEES
ENGLAND	117	81	309	507	69%
SCOTLAND		4	130	134	18%
NORTHERN IRELAND		9	48	57	8%
WALES		10	30	40	5%

4. Responses to our Call for Evidence

Those who provided the Review with written evidence during or after the Call for Evidence period.

Individuals

- Professor John Abraham
- Dr Wael Agur
- Dr Vincent Argent
- Tobias Arndt
- Dr Gottfried Arnold
- Dr Jeffrey K Aronson
- Professor Jill Clayton-Smith, Dr Rebecca Bromley, Professor Peter Turnpenny, Professor Amanda Wood
- Dr Jan Willem Cohen Tervaert
- Dr Chris DeArmitt
- Dr Frances Elmslie
- Jason Farrell (Sky News)
- Professor David Healy
- Professor Carl Heneghan
- Matthew Hill (BBC)
- Dr Vladimir Iakovlev
- Professor Justin Keen, Ms Julia Lake, Dr Susan Partridge, Dr Rebecca Randell
- Professor Vikram Khullar
- Beate Kirk
- Maria Klein-Schmeink MP
- Professor Tim Lewens
- Ken Lownds
- Dr Elena Mancuso
- Kim Morley
- Dr Jesse Olszynko-Gryn
- Myra Robson
- Professor Stefan Roth
- Jonathan Sher
- Mr Mark Slack
- Professor David Taylor
- Dr Neil Vargesson
- Professor Charles Vincent

Patient groups

- Association for Children Damaged by Hormone Pregnancy Tests
- FACSaware
- Independent Fetal Anti-Convulsant Trust (INFACT) and Independent Fetal Anti-Convulsant Syndrome Association (FACSA)
- Mashed Up By Mesh
- Mesh Ireland
- Mesh UK Charitable Trust
- Meshies United Group UK
- Organisation for Anti-Convulsant Syndrome
- Organisation for Anti-Convulsant Syndrome Ireland
- Sling the Mesh
- Welsh Mesh Survivors Support Group

Professional bodies

- Association of British Health Tech Industries
- Association of British Neurologists
- British Association for Community Child Health
- British Association of Urological Surgeons
- British Pain Society
- British Society of Urogynaecology
- Chartered Society of Physiotherapy
- Pelvic Floor Society, and Association of Coloproctology of Great Britain and Ireland
- Prescription Medicines Code of Practice Authority
- Royal College of Anaesthetists
- Royal College of General Practitioners
- Royal College of Obstetricians and Gynaecologists
- Royal College of Psychiatrists
- Royal Pharmaceutical Society

Registries

- National Congenital Anomaly and Rare Disease Registration Service
- National Joint Registry for England, Wales, Northern Ireland and the Isle of Man

Regulators

- General Medical Council
- General Pharmaceutical Council
- Nursing and Midwifery Council

Public bodies

- Care Quality Commission
- Commission on Human Medicines
- Expert Working Group on Hormone Pregnancy Tests
- Medicines & Healthcare products Regulatory Agency
- National Institute for Health and Care Excellence
- National Institute for Health Research
- NHS Digital
- NHS England
- NHS Improvement
- NHS Resolution

Manufacturers of sodium valproate

- Sanofi

Manufacturers of mesh

- Boston Scientific
- Ethicon
- FEG Textiltechnik
- Medtronic

Manufacturers of hormone pregnancy tests

- Bayer

Political stakeholders

- Department of Health and Social Care
- Scottish Government

Specialist mesh units

- 17 of the 26 specialist mesh centres contacted as part of our call for evidence responded with evidence in the form of replies to a series of targeted questions. The evidence was published on the agreement that units were anonymised.

Other organisations

- Association of British Pharmaceutical Industry
- British Medical Journal
- Drug Safety Research Unit
- Epilepsy Action
- Epilepsy Society
- Healthcare Quality Improvement Partnership
- Independent Health Sector Complaints Adjudication Service
- Independent Healthcare Providers Network
- Office of the Chief Coroner
- Private Healthcare Information Network
- UK Teratology Information Service

The following acknowledged the Call for Evidence but did not submit any written evidence:

*** attended an oral hearing**

Individuals

- Dr Sohier Elneil*

Registries

- Breast and Cosmetic Implant Registry
- National Pulmonary Hypertension Audit
- Out of Area Placements

Regulators

- Professional Standards Authority*

Manufacturers of sodium valproate

- Crescent Pharma Limited
- Lupin (Europe) Limited

Manufactures of mesh

- Covidien/Sofradim (now Medtronic)

Manufacturers of hormone pregnancy tests

- Alinter Group (Wallace Manufacturing Chemist Ltd)
- Sanofi

The following did not respond to the Call for Evidence:*** attended an oral hearing****Individuals**

- Professor Peter Kay
- Professor Sheila MacNeil

Professional bodies

- Association for Continence Advice
- Royal College of Midwives
- Royal College of Occupational Therapy
- Royal College of Paediatrics and Child Health
- Royal College of Physicians
- Royal College of Surgeons*
- United Kingdom Continence Society

Registries

- Congenital Anomaly Register & Information Service
- National Audit of Cardiac Rehabilitation
- National Bowel Cancer Audit
- National Diabetes Audit
- National Diabetes Foot Care Audit
- National Diabetes Inpatient Audit
- National Diabetes Inpatient Audit – Harms
- National Diabetes Transition Audit
- National Oesophago-Gastric Cancer Audit
- National Pregnancy in Diabetes Audit
- NHS Safety Thermometer
- Patient Experience of Diabetes Services
- UK Epilepsy and Pregnancy Register*

Regulators

- Health and Care Professions Council

Public bodies

- European Medicines Agency

Manufacturers of sodium valproate

- Concordia International
- Desitin Arzneimittel GMBH
- Desitin Pharma Ltd
- G L Pharma GMBH
- Noriderm Enterprises Limited
- Wockhardt Ltd
- Zentiva

Manufacturers of mesh

- A.M.I Agency for Medical Innovations
- ABISS
- Aesculap (BBRAUN)
- American Medical Systems AMS Ltd ASTORA PAR
- Aspide Medical
- B Braun
- Becton, Dickinson & Co
- BioCer Entwicklungs GmbH
- Caldera Medical
- CL Medical
- Coloplast
- Cook Medical
- Cory Medical
- Cousin Biotech
- DIMA SL
- Lifecell Corp (owned by Allergan)
- Mantis Surgical
- Neomedic
- PAR-Astora
- Piramal (acquired Nicholas Laboratories)
- Purple Surgical
- Serag-Wiessner

Manufacturers of hormone pregnancy tests

- Merck
- Marshalls Pharmaceuticals Ltd
- Pfizer (Parke Davis)

Other organisations

- Action against Medical Accidents*

Political stakeholders

- APPG on Hormone Pregnancy Tests*
- APPG on Valproate and Other Anti-Epileptic Drugs in Pregnancy*
- APPG for Surgical Mesh Implants*
- Department of Health – Northern Ireland
- Health Select Committee
- Liberal Democrat Health Team
- NHS Wales
- Office of the Secretary of State for Northern Ireland
- Parliamentary and Health Service Ombudsman
- Plaid Cymru Health Team
- Shadow Health Team
- Stormont Executive
- Welsh Government

5. Oral hearings

Overview

Total number of hearing days held from November 2018 to May 2019	23
Total number of sessions held across those hearing days	78

Number of attendances (to one or more session) by category	
Patient groups	14
All-Party Parliamentary Groups	3
Professional associations, colleges and societies	11
Provider organisations – NHS and private	9
Independent healthcare professionals: clinicians and allied health	10
Content experts and discussants	6
Charities	7
Registers/registries	3
Pharmaceutical companies	2
Professional regulatory bodies	3
Industry trade bodies	1
Department of Health and Social Care and its agencies or partner organisations	8

List of attendees at the oral hearings

Patient Groups	1. FACSaware 2. Mashed up by Mesh 3. Mesh UK Charitable Trust 4. Meshies United Group UK 5. Mesh Ireland 6. Welsh Mesh Survivors Support Group 7. Scottish Mesh Survivors 8. Association for Children Damaged by Hormone Pregnancy Tests 9. Independent Fetal Anti-Convulsant Trust/Fetal Anti-Convulsant Syndrome Association 10. Sling the Mesh 11. Valproate Victims 12. Organisation for Anti-Convulsant Syndrome 13. Organisation for Anti-Convulsant Syndrome – Ireland 14. Young People Affected by Valproate	14
APPGs	1. Hormone Pregnancy Tests All Party-Parliamentary Group 2. Valproate and Other Anti-Epileptic Drugs in Pregnancy All-Party Parliamentary Group 3. All-Party Parliamentary Group on Surgical Mesh Implants	3
Professional Associations, Colleges and Societies	1. Royal College of General Practitioners 2. Association of British Neurologists 3. Royal College of Psychiatrists 4. Royal Pharmaceutical Society 5. Chartered Society of Physiotherapy 6. British Pain Society 7. British Association of Urological Surgeons 8. British Society of Urogynaecology 9. Pelvic Floor Society 10. Royal College of Surgeons 11. Royal College of Obstetricians and Gynaecologists	11

Provider organisations	1. South Tees Hospitals NHS Foundation Trust 2. Central Manchester University Hospitals NHS Foundation Trust 3. King's College Hospital NHS Foundation Trust 4. Oxford University Hospitals NHS Foundation Trust 5. Epsom and St Helier University Hospitals NHS Trust 6. BMI Healthcare 7. Nuffield Health 8. Spire Healthcare 9. Private Healthcare Information Network	9
Independent healthcare professionals: clinicians and allied health	1. Dr Rebecca Bromley 2. Professor Jill Clayton-Smith 3. Professor Peter Turnpenny 4. Dr Wael Agur 5. Ms Sohier Elneil 6. Myra Robson 7. Dr Frances Elmslie 8. Dr Vincent Argent 9. Mr Mark Slack 10. Professor Shakila Thangaratinam	10
Content experts and discussants	1. Dr Jesse Olszynko-Gryn 2. Professor Carl Heneghan 3. Professor John Abraham 4. Professor Neil Vargesson 5. Professor Justin Keen 6. Jason Farrell	6
Charities	1. Epilepsy Society 2. Epilepsy Action 3. vCJD Trust 4. Thalidomide Trust 5. Healthcare Quality Improvement Partnership 6. Action against Medical Accidents 7. Drug Safety Research Unit	7
Registers/registries	1. The National Congenital Anomaly and Rare Disease Registration Service 2. National Joint Registry 3. UK Epilepsy and Pregnancy Register	3
Pharmaceutical and device manufacturers	1. Sanofi UK 2. FEG Textiltechnik	2

Professional regulatory bodies	1. General Medical Council 2. General Pharmaceutical Council 3. Professional Standards Authority	3
Industry trade bodies	1. Association of British HealthTec Industries 2. Independent Healthcare Providers Network	2
Department of Health and Social Care (DHSC) and its agencies or partner organisations	1. Medicines and Healthcare Products Regulation Agency 2. National Institute for Health and Care Excellence 3. NHS England 4. NHS Digital 5. Care Quality Commission 6. NHS Improvement 7. Department of Health and Social Care 8. NHS Resolution 9. The Commission on Human Medicines, Expert Working Group on Hormone Pregnancy Tests	9

6. Review meetings (in person or by telephone)

In addition to the formal evidence sessions and formal patient group feedback events.

With AFFECTED INDIVIDUALS AND PATIENT GROUP REPRESENTATIVES	
May/June 2018	PRIMODOS: Association for Children Damaged by Hormone Pregnancy Tests SODIUM VALPROATE: FACSaware Independent Fetal Anti-Convulsant Syndrome Association (INFACT)/ Fetal Anti-Convulsant Syndrome Association (FACSA) Organisation for Anti-Convulsant Syndrome (OACS) and OACS Ireland PELVIC MESH: Mashed Up by Mesh Meshies United Group UK Sling the Mesh
June 2018	Ms Cat Lee – mesh affected patient
July 2018	Group of young people affected by Sodium Valproate
	Sling the Mesh (accompanied by Miss Sohler Elneil: Consultant Urogynaecologist and Uro-neurologist, UCLH)
	Meshies United Group UK
August 2018	Deborah Mann: mother of young person affected by Sodium Valproate
Sept 2018	Mesh Ireland
Dec 2018	Mesh UK Charitable Trust
July 2019	INFACT/FACSA and representatives of Foetal Anticonvulsant Syndrome New Zealand
August 2019	Valproate Victims, Dr Jess Ozlynsko-Grynn: Lecturer in Health and Well Being and Bridgette York: Member, Patients in Involved in National Institute for Excellence (NICE)
Throughout the Review	Where meeting face to face was not practical or possible, the Review held telephone conversations with a number of individuals and patient group representatives.

With ALL-PARTY PARLIAMENTARY GROUPS (APPGs)	
May/June 2018	All-Party Parliamentary Group (APPG) on Surgical Mesh Implants: Owen Smith MP, Chair and other members
	All-Party Parliamentary Group (APPG) on Valproate and Other Anti-Epileptic Drugs in Pregnancy: Norman Lamb MP, Chair and other members
	All-Party Parliamentary Group (APPG) on Hormone Pregnancy Tests, Yasmin Qureshi MP, Chair and other members
Oct 2018	APPG on Valproate and Other Anti-Epileptic Drugs in Pregnancy: Norman Lamb MP, Chair and INFACT and FACSA: Emma Murphy and Janet Williams
Dec 2018	APPG on Valproate and Other Anti-Epileptic Drugs in Pregnancy: Norman Lamb MP, Chair, INFACT and FACSA: Emma Murphy and Janet Williams and Lord O'Shaughnessy: former Parliamentary Under Secretary for Health
Feb 2019	APPG on HPTs: Yasmin Qureshi, MP Chair and other members, Marie Lyon Chair of the ACDHPT
March 2020	APPG on HPTs: Yasmin Qureshi, MP Chair and other members, Marie Lyon Chair of the ACDHPT

With CLINICIANS/PROFESSIONAL COLLEGES/NHS TRUSTS	
May/June 2018	Mr Neil Mortensen: Colorectal Surgeon and Vice President, Royal College of Surgeons
	Professor David Baldwin: Chair, Psychopharmacology Committee, Royal College of Psychiatrists
	Ms Swati Jha: Vice Chair, British Society of Urogynaecology & Professor Linda Cardozo, Consultant Gynaecologist
	Professor Shakila Thangaratnam, Professor of Maternal and Perinatal Health and Consultant Obstetrician
July 2018	Dr Frances Elmslie: Consultant Clinical Geneticist and Chair of National Clinical Reference Group for Genetics
	Dr Andrew Kelso, Consultant Neurologist
August 2018	Myra Robson: Senior Pelvic Health Physiotherapist
	Mr Neil Mortensen
	Sir Colin Berry: Pathologist (retired)
September 2018	Mr Chris Harding: Consultant Urological Surgeon and Chair, British Association of Urological Surgeons subsection of Female, Neurological and Urodynamic Urology

With CLINICIANS/PROFESSIONAL COLLEGES/NHS TRUSTS	
October 2018	Mr Mark Slack: Consultant Gynaecologist and Urogynaecologist
	Professor Jonathan Duckett: Chair, British Society of Urogynaecology and Ms Swati Jha
November 2018	Mr Andrew Williams: Colorectal Pelvic Floor Surgeon and Chair of Pelvic Floor Society
April 2019	Professor Charles Vincent: Emeritus Professor of Clinical Safety Research
June 2019	Dr Dionysios K Veronikis: Specialist in Vaginal Surgery, Urogynaecology and Vaginal Mesh Complications
	University College London Hospitals NHS Foundation Trust: Baroness Julia Neuberger, Chair and Professor Marcel Levi, Chief Executive
September 2019	Mr Vikram Khullar: Consultant Obstetrician and Gynaecologist Professor of Urogynaecology

With DEPARTMENT OF HEALTH AND SOCIAL CARE (DHSC) and its AGENCIES or PARTNER ORGANISATIONS	
July 2019	Department of Work and Pensions: Representatives
Nov 2019	NHS England: John Stewart, Acting Director of Specialised Commissioning and Anthony Prudhoe, Senior Manager, Programme of Care Women and Children
Dec2019/Jan 2020	NHS England: Professor Stephen Powis, National Medical Director
Dec2019/Jan 2020	NHSX: representatives
Jan 2020	MHRA: Dr June Raine, Chief Executive Officer and Louise Loughlin, Head of Science Strategy
April 2020	Medicines and Medical Devices Bill Drafting Team: Representatives
May 2020	MHRA: Dr June Raine, Chief Executive Officer, Graeme Tunbridge, Director of Devices, and Louise Loughlin, Head of Science Strategy
May 2020	NHS England Specialised Commissioning: Anthony Prudhoe, Senior Manager, Programme of Care Women and Children
May 2020	NHS Digital: Jem Rashbass, Executive Director: Master registries and data and other Representatives
June 2020	Medicines and Medical Devices Bill Drafting Team: Representatives
Throughout the Review	Department of Health and Social Care: sponsor representatives

With OTHER GROUPS, ORGANISATIONS AND INDIVIDUALS	
May 2018	Dr Catherine Calderwood, Chief Medical Officer for Scotland Ms Mikey Argy, Thalidomide Campaigner
July 2018	GS1 UK: Professor Duncan Eaton, Chair of Healthcare Advisory Board and Claire Clarke, Engagement Manager
March and May 2019	Sanofi: representatives
May/Sept/Nov 2019	Lord James O'Shaughnessy and Harry Cayton: former Chief Executive of Professional Standards Authority
June 2019	Lord O'Shaughnessy and Adam Sampson: Consultant and former Legal Ombudsman Sarah Wilkinson, NHS Digital; Matt James, Private Healthcare Information Network; Celia Ingham-Clark and Stephen Anderson, NHS England/NHS Improvement and Professor Timothy Rockall, Royal College of Surgeons
Sept 2019	Dr Chris DeArmitt: Chartered Chemist; Dr Vladimir Lakovlev: Associate Professor, University of Toronto; Dr Jan Willem Cohen Tervaert: Professor, University of Alberta; Professor Vikram Khullar: Consultant Urogynaecologist, Imperial College Healthcare Trust, and Mr Mark Slack: Consultant Urogynaecologist, Cambridge University Hospitals
Nov 2019	Rt Hon Jeremy Hunt, MP Professor Stefan Roth: Professor of Mechanical Engineering, Schmalkalden University Sir Liam Donaldson, former Chief Medical Officer DHSC Emily Frith: Office of Children's Commissioner Dr Catherine Calderwood, Chief Medical Officer for Scotland
Dec 2019	General Pharmaceutical Council: Representatives
April 2020	GMC: Dame Claire Marx, Council Chair, Charlie Massey, Chief Executive and Registrar, and Paul Buckley, Director of Strategy and Policy

7. Independent Medicines and Medical Devices Safety Review

Secretariat

Dr Valerie Brasse – Secretary to the Review (March 2018 – July 2020)

Donna Boreham-Downey – Deputy Secretary to the Review (July 2018 – March 2020)

Dr Sonia Macleod – Lead Researcher (June 2018 – July 2020)

Mel Ramasawmy – Information Manager and Senior Researcher (July 2018 – March 2020)

Howard Dayle – Business Manager (June 2018 – July 2020)

Orla Daly – Research Officer (July 2018 – February 2019)

Jordan Charlesworth – Research Officer (February 2019 – March 2020)

Elizabeth Dickson – Support Officer (January 2019 – March 2020)

Legal Representatives

Pryesh Patel – Lawyer (June 2018 – January 2019)

Joanna Wood – Lawyer (January 2019 – July 2020)

Fenella Morris QC – Counsel (November 2018 – July 2020)

Paul Mertens – Counsel (December 2018 – July 2020)

Communications

The team at Luther Pendragon (February 2018 – July 2020)

Appendix 6: Abbreviations

A&E	Accident & Emergency
AAGL	Association of Gynecologic Laparoscopists
ABN	Association of British Neurologists
ACC	Accident Compensation Corporation
ACOG	American College of Obstetricians and Gynecologists
ADHD	Attention deficit hyperactivity disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AED	Antiepileptic Drug
AFS	Autologous Fascial Sling
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé
ANSM	Agence Nationale de Sécurité du médicament et des produits de santé
APPG	All-Party Parliamentary Group
ARTG	Australian Register of Therapeutic Goods
ASD	Autism Spectrum Disorders
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
ASIA	Autoinflammatory/Autoimmunity Syndrome Induced by Adjuvants
AUGS	American Urogynecologic Society
BAUS	British Association of Urological Surgeons
BFLUTS	Bristol Female Lower Urinary Tract Symptoms
BMA	British Medical Association
BPNA	British Paediatric Neurology Association
BSUG	British Society of Urogynaecology
CAG	Clinical Advisory Group
CAM	Chorioallantoic membrane
CAS	Central Alerting System
CDC	Centers for Disease Control and Prevention (USA)
CE	Conformité Européenne
CHM	Commission on Human Medicines

CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CMO	Chief Medical Officer
CRM	Committee on Review of Medicines (est. 1975)
CSD	Committee on Safety of Drugs
CSD/AR	Committee on Safety of Drugs, Adverse Reactions Sub-committee
CSI	Company core safety information
CSM	Committee on Safety of Medicines
CSM/AR	Committee on Safety of Medicines, Adverse Reactions Sub-committee
DCS	Decision Conflict Scale
DEAC	Devices Expert Advisory Committee
DH	Department of Health
DHPC	Dear Healthcare Professional Communication
DHSC	Department of Health and Social Care
DHSS	Department of Health and Social Security
DUS	Drug Utilisation Study
EC	European Commission
ECM	Extracellular Matrix
EMA	European Medicines Agency
E-TOT	Evaluation of TransObturator Tension-free Vaginal Tapes
EU	European Union
EURAP	European Registry of Antiepileptic Drugs and Pregnancy
EWG	Expert Working Group
FACS	Fetal Anti-Convulsant Syndrome
FAQ	Frequently Asked Questions
FBR	Foreign Body Reaction
FDA	Food and Drug Administration
FDA	Food and Drug Administration (USA)
GMC	General Medical Council
GP	General Practitioner
GPRD	General Practice Research Database
HCP	Healthcare Professional
HES	Hospital Episode Statistics
HQIP	Healthcare Quality Improvement Partnership

HRQOL	Health-related Quality of Life
HSCIC	Health & Social Care Information Centre (now NHS Digital)
HSE	Health Service Executive
IFU	Instructions For use
IGAS	Inspection Générale des Affaires Sociales (France)
IIQ-7	Incontinence Impact Questionnaire - Short Form
IMMDSR	Independent Medicines & Medical Devices Safety Review
IPAC	Interventional Procedures Advisory Committee
IUGA	International Urogynecological Association
IVS	Intravaginal Slingplasty
MAUDE	Manufacturer and User Facility Device Experience
MCA	Medicines Control Agency
MDA	Medical Devices Agency
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MMDR	Medicines and Medical Devices Regulation
MMP	Matrix Metalloproteinase
MP	Member of Parliament
MUS	Midurethral Sling
MUT	Midurethral Tape
NAFC	National Association For Continence
NGO	Non-governmental Organisation
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NRLS	National Learning and Reporting System
NTD	Neural Tube Defect
OPCS	Office of Population Censuses and Surveys
PDA	Patient Decision Aid
PET	Poly(ethylene terephthalate)
PFS	Pelvic Floor Society
PHN	Public Health Notification
PhVWP	Pharmacovigilance Working Party (of the European Medicines Agency)
PIL	Patient information leaflet
PMA	Premarket Approval

POP	Pelvic Organ Prolapse
PP	Polypropylene
PPP	Pregnancy Prevention Plan
PRAC	Pharmacovigilance Risk Assessment Committee (EU)
PSUR	Periodic Safety Update Report
PVDF	Polyvinylidene fluoride
Q1	Quarter 1
QOF	Quality and Outcomes Framework
R&C	Reckitt and Colman
RCOG	Royal College of Obstetricians and Gynaecologists
RCOG	Royal College of Obstetricians and Gynaecologists
RCP	Royal College of Physicians
RCPCH	Royal College of Paediatrics and Child Health
RCPsych	Royal College of Psychiatrists
RCT	Randomised Control Trial
RR	Relative Risk or Risk Ratio
SBAR	Situational Background Assessment and Recommendation
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SEM	Scanning Electron Microscopy
SERNIP	Safety and Efficacy Register for New Interventional Procedures
SFNUU	Section of Female, Neurological & Urodynamic Urology
SFRU	Section of Female and Reconstructive Urology
SmPC	Summary of Product Characteristics
SMUS	Synthetic Midurethral Sling
SS	Suprapubic Sling
SUFU	Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction
SUI	Stress Urinary Incontinence
TFU	Tension-free Urethropexy
TGA	Therapeutic Goods Administration
TGA	Therapeutic Goods Administration, Australia
TOT	Transobturator Tape
TVT	Trans-Vaginal tape
TVT-O	Trans-Vaginal Tape - Obturator
TVT-S	TVT-Secur

UK	United Kingdom
USA	United States of America
VMR	Ventral Mesh Rectopexy
WHIG	Women's Health Implementation Group

Appendix 7: Glossary

(Secondary) Amenorrhea	Amenorrhoea is the absence or cessation of menstruation. It can be divided into two types: primary and secondary amenorrhoea. Secondary amenorrhoea is the cessation of menstruation in women with previous menses. Definitions vary as to how long, but involve the cessation of menses for 3-6 months, in women with previously normal menstruation.
Abortifacient	A drug or other agent that causes the premature termination of pregnancy.
Bilateral Cholesteatoma	The presence of keratinising squamous epithelium within the middle ear, or in other pneumatised areas of the temporal bone. Affecting both sides.
Colposuspension	A surgical treatment for stress urinary incontinence, involving the suture fixation of the lower part of the front of the vagina to the Cooper ligament (behind the pubic bone) on each side. This helps to lift the bladder neck upwards, improving pressure transmission and compression of the bladder neck. This can be performed as an open, or laparoscopic procedure.
Contraindication	A sign that someone should not continue with a particular medicine or treatment because it is or might be harmful.
Cystocele	Otherwise known as an ‘anterior prolapse’ – a form of pelvic organ prolapse that involves the bladder prolapsing into the vagina, due to weakening of the supportive tissue between the bladder and vaginal wall.
Database	A structured set of data held in a computer, especially one that is accessible in various ways.
Dyspareunia	Abnormally difficult or painful sexual intercourse.
Electrospinning	A method to produce ultrafine (in nanometres) fibres by charging and ejecting a polymer solution through a spinneret under a high-voltage electric field and to solidify or coagulate it to form a filament.
Gaslighting	To manipulate (a person) by psychological means into questioning his or her own sanity.
Health and Social Care Select Committee	A committee appointed by the House of Commons to examine the policy, administration and expenditure of the Department of Health and Social Care and its associated bodies.

Iatrogenic	(of a medical disorder) caused by the diagnosis, manner, or treatment of a physician.
Immunoassay	A highly selective bioanalytical method that measures the presence or concentration of analytes, ranging from small molecules to macromolecules, in a solution through the use of an antibody or an antigen as a biorecognition agent.
Munchausen by proxy	A psychological disorder in which a parent and typically a mother harms her child (as by poisoning), falsifies the child's medical history, or tampers with the child's medical specimens in order to create a situation that requires or seems to require medical attention.
Obturator foramen	A large oval or irregularly triangular aperture in the hip bone, the margins of which are formed by the pubis and the ischium; it is closed in the natural state by the obturator membrane, except for a small opening for the passage of the obturator vessels and nerve.
Oestrogen	A female steroid hormone that is produced by the ovaries and, in lesser amounts, by the adrenal cortex, placenta, and male testes. Oestrogen helps to control and guide sexual development, including the physical changes associated with puberty. It also influences the course of ovulation in the monthly menstrual cycle, lactation after pregnancy, aspects of mood, and the aging process.
Ombudsman	An ombudsman is an official who investigates complaints (usually lodged by private citizens) against businesses, public entities, or officials.
Orofacial cleft	A term encompassing cleft lip and cleft palate, which are openings or splits in the upper lip, the roof of the mouth (palate) or both. Cleft lip and cleft palate result when facial structures that are developing in an unborn baby don't close completely.
Oxidise	The combination of a substance with oxygen, the loss of electrons or hydrogen, or the formation of an oxide.
Pelvic Organ Prolapse	Pelvic Organ Prolapse happens when the muscles and tissues supporting the pelvic organs (the uterus, bladder, or rectum) become weak or loose. This allows one or more of the pelvic organs to drop or press into or out of the vagina. This can involve the womb (uterus), bowel, bladder or top of the vagina.
Polymer	A chemical compound with large molecules made of many smaller molecules of the same kind. Some polymers exist naturally, and others are produced synthetically.

Polypropylene	A synthetic resin formed from the polymerisation of propylene. Polypropylene is moulded or extruded into many plastic products in which toughness, flexibility, light weight, and heat resistance are required. It can also be spun into fibres.
Progestogen	Any of a group of steroid hormones that have progesterone-like activity, used in oral contraceptives and in treating gynaecological disorders.
Prophylaxis	The prevention of disease or control of its possible spread.
PVDF – Polyvinylidene fluoride	A semi-crystalline, high purity thermoplastic fluoropolymer. PVDF is generally synthesized by the free radical polymerization of 1,1-difluoroethylene.
Rectocele	Also known as ‘posterior prolapse’ – a form of pelvic organ prolapse in which the thin wall of tissue that separates the rectum from the vagina weakens, allowing the rectum to prolapse into the vagina.
Registry	An organised system that continuously and consistently collects relevant data in conjunction with routine clinical care, evaluates meaningful outcomes and comprehensively covers the population defined by exposure to a particular medical device(s) at a reasonably generalised scale (e.g. national, regional, health system) with a primary aim to improve the quality of patient care.
Spina bifida	A condition in which the neural tube, a layer of cells that ultimately develops into the brain and spinal cord, fails to close completely during the first few weeks of embryonic development. As a result, when the spine forms, the bones of the spinal column do not close completely around the developing nerves of the spinal cord. Part of the spinal cord may stick out through an opening in the spine, leading to permanent nerve damage. Because spina bifida is caused by abnormalities of the neural tube, it is classified as a neural tube defect.
Stress Urinary Incontinence	The unintentional passing of urine at times when the bladder is under pressure; for example, whilst coughing, laughing or exercising.
Teratogen	Any agent that causes an abnormality following foetal exposure during pregnancy.
Variant CJD	A neurological disease classed as a Transmissible Spongiform Encephalopathy. The disease is caused by misfolded proteins known as prions, which form aggregates in neurological tissue, leading to progressive brain damage and eventual death.
Virilisation	The abnormal development of male sexual characteristics in a female, usually as the result of hormone therapies or adrenal malfunction.
Whitewash	An attempt to stop people finding out the true facts about a situation.

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