

A summary of the evidence on the benefits and risks of vaginal mesh implants

28 October 2014

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Executive summary

Women have reported serious and debilitating problems following surgical treatment for stress urinary incontinence (SUI) or pelvic organ prolapse (POP) using vaginal mesh implants. Although the number of reports to MHRA is low compared to the overall use of these implants, there is some evidence of under-reporting and there are concerns that MHRA is not aware of all women who have experienced problems.

The Chief Medical Officer of England has asked MHRA to review the evidence from the regulatory system on the benefits and risks of vaginal mesh implants.

Our use of the term 'safety data' throughout this report is defined in two ways: pre-market safety data and post-market safety data. Pre-market safety data refer to information included in the manufacturer's technical file. This includes toxicity data, clinical and preclinical data, risk assessment and quality systems. Post-market safety data refers to information about the safety and performance of the device gathered by the manufacturer about the device in use. Some of this post-market safety data will meet the criteria for vigilance and will need to be reported to the competent authority (CA).

Throughout this report we have referred to 'vaginal mesh implants'. The term vaginal mesh implant is intended to include vaginal mid-urethral tapes used to treat SUI and vaginal mesh used to treat POP, made of polypropylene. These are permanent implants and are not intended to be removed. It should also be recognised that although SUI and POP can be both treated with mesh implants, they are two distinct clinical conditions.

As the UK CA, MHRA manages the operation of the European Union regulatory system for medical devices within the UK. Primarily the manufacturer is responsible for the safety and performance of the device. For some higher risk devices, notified bodies (designated and monitored by a CA) will assess the manufacturer's quality system and sample the technical and clinical data before the device is placed on the market. However, the role of the CA in assessing the safety of devices in use is mostly post-market. In light of these constraints, MHRA is actively engaged in the strengthening of the regulatory system and has evaluated whether known challenges, such as variation in the quality and scrutiny of notified bodies, could affect the confidence of our advice in this report. We are satisfied that these factors have had no impact on our conclusions.

We recognise that the statement 'the benefit outweighs the risk' may be interpreted differently from the regulatory view by individual patients, patient groups and healthcare professionals. From our review of the information available to us, there appears to be no evidence that vaginal mesh implants are unsafe, which would justify MHRA taking enforcement action to take them off the market, or remove them from use.

In considering the overall risk–benefit balance of vaginal mesh implants for SUI, no single conclusion is given as to how successful the treatment option is, as this depends on different surgical approaches. Data from literature in the National Institute for health and Care Excellence (NICE) guideline CG171 (see Section 5.3.3) show that up to one year post-operation for procedures involving vaginal mesh implants for SUI, peri-operative complications can be in the range of 1-12%, depending upon the surgical approach. More limited data at 10 years post-operation indicate that significant long-term benefits are achieved in the majority of women undergoing these procedures, which denominator data indicates to be currently around 13,500 women per year in England. Thus the overall benefit outweighs the relatively low rate of complications.

The data on outcomes for vaginal mesh implants used to treat POP are more varied, reflecting the various procedures currently used. NICE guidance for the various POP procedures gives evidence that for particular procedures, vaginal mesh implants can offer significant improvements in failure rates compared with surgical repairs undertaken without the use of mesh.

Most POP guideline documents give evidence on the efficacy and safety of the procedures available. However, for most of the procedures, they state that the evidence is inadequate in quantity and quality. They do not state that vaginal mesh implants should not be used, but does state that vaginal mesh implant procedures should only be used with special arrangements for clinical governance, consent and audit or research.

Data from published literature indicate that adverse events occur with a frequency of, on average, 6.5% or below, with the exception of deterioration of sexual function, which occurs on average in 15.3% or below. Given the benefits seen, the overall benefits appear to outweigh the risks. However, further work needs to be done to characterise long-term safety in relation to different surgical procedures and vaginal mesh implant types. We propose that this work should be considered by the NHS England led working group, recognizing that research is already underway as part of the PROspect trial (see Section 8.4.1).

MHRA's current position is that, for the majority of women, the use of vaginal mesh implants is safe and effective. However, as with all surgery, there is an element of risk to the individual patient. This conclusion is entirely dependent on compliance with NICE and other sources of guidance, which emphasise the caution that should be exercised prior to surgery being considered. Whilst some women have experienced distressing and severe effects, the current evidence shows that when these products are used correctly they can help alleviate the very distressing symptoms of SUI and POP and as such the benefits still outweigh the risks.

Other issues associated with the use of these devices such as informed patient consent and suitable patient selection, are being taken forward by the NHS England led working group on vaginal mesh implants.

Although this summary of the available evidence has not changed our opinion, MHRA will continue to keep vaginal mesh implants under enhanced scrutiny. We recognise that there are many uncertainties surrounding this issue which need addressing. We review and revise our position regularly, particularly in light of new information from the wide variety of sources reviewed in this document and others which may become available in the future.

We are awaiting the outcome of the reviews by the European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), and are contributing to the Scottish Government and the work of the NHS England led working group. Further action may be taken if emerging evidence supports a change in position.

In line with other medical device regulators worldwide we are not aware of a robust body of evidence to suggest that these devices are unsafe if used properly as intended and therefore should be removed from the market.

Glossary

ABHI	Association of British Healthcare Industries
AIMS	Adverse Incident Tracking System
BAUS	British Association of Urological Surgeons
BSUG	British Society of Urogynaecology
CA	Competent authority
CCG	Clinical Commissioning Group
CSD	Committee on Safety of Devices
CSP	Chartered Society of Physiotherapy
DA	Devolved administration (e.g. Northern Ireland, Scotland and Wales)
DH	Department of Health
EC	European Commission
EU	European Union
EUGA	European Urogynaecological Association
FCE	Finished consultant episode
FDA	Food and Drug Administration (in the United States)
GMC	General Medical Council
HES	Hospital episode statistics
HSCIC	Health and Social Care Information Centre
IFU	Instructions for use
IUGA	International Urogynaecological Association
IVS	Intravaginal slingplasty
MDD	Medical Devices Directives
MDR	Medical Devices Regulations
MDSO	Medical Device Safety Officer
MHRA	Medicines and Healthcare Products Regulatory Agency
MSO	Medication Safety Officer
MUS	Mid-urethral slings
NBOG	Notified Bodies Operations Group
NICE	National Institute for health and Care Excellence
NPSA	National Patient Safety Agency
NRLS	National Reporting & Learning System
RCOG	Royal College of Obstetricians & Gynaecologists
RCS	Royal College of Surgeons
RCT	Randomised controlled trial
PMS	Post-market surveillance
POP	Pelvic organ prolapse
PSA	Patient Safety Alerts
SCENIHR	European Scientific Committee on Emerging and Newly Identified Health Risks
SPARC	Supra pubic arch sling
SR	Systematic review
SUI	Stress urinary incontinence
TGA	Therapeutic Goods Administration (in Australia)
TOT	Transobturator sling
TVT	Tension-free vaginal tape
TVT-O	Tension-free vaginal tape (obturator)
UDI	Unique device identifier

Introduction

1.1 Introduction and overview

In June 2014, the Department of Health's Chief Medical Officer requested a report from MHRA as the regulator of medical devices, to advise on whether the risk/benefit assessment remains correct for vaginal mesh implants.

This was in light of the recent decision taken by the Scottish Parliament to ask Health Boards to consider the suspension of these devices. An interim report was requested by the end of July 2014 with a full report at the end of August 2014.

MHRA had received very few adverse incident reports indicating problems associated with these mesh devices. However, around 2010 we became aware of increasing concerns about severe adverse effects associated with vaginal mesh implant surgery from patients writing to MHRA and by emerging patient support groups. A patient petition to ban these devices was started in January 2011.

MHRA has been actively investigating reported issues and concerns with these devices, working closely with clinical groups such as Royal College of Obstetricians & Gynaecologists (RCOG), British Society of Urogynaecology (BSUG), British Association of Urological Surgeons (BAUS) and the Department of Health (DH).

We undertook a number of actions to better understand their use and the complications associated with their use. MHRA hosted a workshop in March 2011, looking at issues related to vaginal mesh implants used to treat SUI and a second workshop in March 2012 on vaginal mesh implants used to treat POP. Participants included representatives from RCOG, BSUG and BAUS, NICE, manufacturers and a notified body.

To support our investigations we have:

- consulted individual clinicians and professional clinical associations
- met with patient support group representatives
- consulted and liaised with other European Union (EU) countries and the Food and Drug Administration (FDA) in the United States.
- taken part in the European Commission (EC) Task Force Group on vaginal mesh implants
- engaged with DH, NHS England and the devolved administrations (DA) to take forward various initiatives related to professional guidance, patient information leaflets and proposals for registries.

MHRA funded a major piece of work, in 2012, to inform our understanding of vaginal mesh implant related issues and our current view on the safety of these devices. This independent review by York University Health Economics Consortium of up-to-date published evidence of problems associated with vaginal mesh implants is known as the 'York Report'.

Information from all these sources above formed the basis of MHRA's view that for the majority of women use of vaginal mesh implants is safe, but as with all surgery, there is an element of risk to the individual patient. Whilst a comparatively small number of women have experienced distressing and severe effects, the current evidence shows that, when these products are used correctly, they can help with the very distressing symptoms of SUI and POP, and as such the benefits still outweigh the risks. In line with other regulators worldwide we have not seen a body of evidence that would indicate that these products should be withdrawn from use.

The key issues associated with the use of these devices appear to be mainly clinical, including identification of suitable patients for the procedures, good surgical technique, informed patient consent and patients not being fully apprised of the possible adverse effects associated with the surgery.

The 'York Report' was published on MHRA's website on 22 November 2012 with a combined DH/MHRA press release. Also, a letter sent from Sir Bruce Keogh to all NHS medical directors (see Annex A) to draw their attention to the report and to ensure familiarity with existing NICE and professional guidance on the safe and appropriate use of vaginal mesh implants was published. A further letter was issued by Sir Bruce Keogh to the NHS in December 2013 (see Annex B) co-signed by relevant clinical associations and colleges, on vaginal mesh implants stating that the pertinent NICE guidelines should be followed and highlighting issues of patient consent, audit, adverse event reporting to MHRA and specialist care for surgery for vaginal mesh implant removal.

1.2 Medical devices regulations and the role of MHRA

All vaginal mesh implants for SUI and POP fall into the definition of a medical device and have to meet the requirements of the Medical Devices Directive (93/42/EEC). These implants must be CE marked before being sold on the European market. The majority of vaginal mesh implants are CE marked Class IIb medical devices, which means a notified body will have sampled across the range of a manufacturer's products and processes to ensure that the essential requirements of the Medical Device Directive (MDD) are being met. The manufacturer's technical files will also be sampled, which will include a review of the risk management file.

The majority of vaginal mesh implants are classified into a medium to high risk category. The manufacturers will have compiled a technical file of safety data of information that demonstrates compliance with the essential requirements described in Annex I of the MDD and would include information on the design and construction of the device, technical specifications, biocompatibility, clinical data, sterilisation, right through to packaging and labelling. Some vaginal mesh implants for POP incorporate an absorbable component and are classified in the high risk category of medical devices and, therefore, will undergo a more rigorous assessment.

The role of MHRA, as the UK CA, is to ensure that all medical devices placed on the UK market are compliant with the relevant legislation and to enforce this legislation on behalf of the Secretary of State. MHRA is responsible for overseeing the activities and ongoing designation of notified bodies within the UK and for operating the UK medical device vigilance system.

Patient safety with medical devices is dependent on the collaborative actions of several key stakeholders, including CAs, manufacturers, notified bodies, healthcare professionals and patients themselves.

1.3 Vaginal mesh implants

There are several types of vaginal mesh implants on the market in Europe. This report focusses on mid-urethral tapes for SUI and vaginal mesh for POP. This report does not contain information related to mesh implants used for abdominal and inguinal hernia repair.

Vaginal mesh implants are permanent implants that are not intended to be removed. They are generally made from non-absorbable polypropylene, derived from non-absorbable sutures, and entwined in a woven or knitted mesh construction. Some vaginal mesh implants may also have a 'biological' absorbable component to assist incorporation with internal body tissues.

They are implanted by surgeons across different specialist fields depending on the extent and nature of the patient's condition: urology, urogynaecology and gynaecology.

1.4 Evidence and data related to safety of vaginal mesh implants

Evidence available to us on the safety of vaginal mesh implants is based on a number of sources including, adverse incident reports, published peer reviewed literature and information from vaginal mesh implant manufacturers, patients and healthcare professionals.

When MHRA first became aware of issues related to vaginal mesh implants from women who had experienced severe adverse events, we had received very few reports of adverse incidents. To better understand the issues related to the safe use of these devices, MHRA hosted two workshops in 2011 and 2012, both chaired by Professor Paul Abrams from the Bristol Urological Institute (BUI), a registered charity based at Southmead Hospital, Bristol. The first workshop's aim was to better understand the use of vaginal mesh implants for SUI and the complications associated with their use. The second workshop was on vaginal mesh implants for POP and discussed regulation, implant use and information for patients. Information related to these workshops was placed on MHRA's website.

1.5 Adverse incident reports and information from patients and manufacturers

MHRA investigates both mandatory adverse event reports from manufacturers (vigilance reports) and adverse events reported voluntarily by healthcare professionals and members of the public (see Section 4). We also receive reports from other CAs from around the world.

Evidence from patients and patient support groups mainly consists of individual patient experiences being reported to MHRA, in the form of adverse incident reports.

The number of reports from members of the public for vaginal mesh implants has increased in the last four years, possibly due to increased awareness of problems women are experiencing with vaginal mesh implants, increased media coverage, and campaigning by patient support groups. Although we have heard some allegations from patient support groups that many more women have been adversely affected by these vaginal mesh implants, the number of reports to MHRA is still relatively low compared to the number of devices we understand have been used.

Patient experiences reported to MHRA mainly include pain, mesh erosion/exposure and infection. Other complications reported include relapse of the condition being treated and sexual difficulties. MHRA's review of these reports indicates that although they may be related to the surgical procedure of implanting the vaginal mesh implant, there has not been any evidence that the implant itself is inherently unsafe.

Very few adverse incident reports have come directly from healthcare professionals. MHRA are making efforts to improve reporting, including work with NHS England's National Reporting and Learning System (NRLS), and with the Devolved Governments (see Section 8.2).

Information from manufacturers has either been provided to MHRA through regulatory obligations to report vigilance incident reports to us, and/or from direct requests for information, such as the manufacturer's clinical evidence of safety and results of their post-market surveillance (PMS) activities. Information has been acquired from one of the UK notified bodies known to have certified vaginal mesh implant manufacturers.

1.6 Number of vaginal mesh implants in use

There is no single database that records how many vaginal mesh implants are implanted or removed within the UK. However, this report contains overall sales figures from manufacturers. The Health and Social Care Information Centre runs the Health Episodes Statistics (HES) database to record details of all admissions, outpatient appointments and A&E attendances at NHS hospitals in England. HES data are a useful indicator of how many operations have taken place in England. It is essentially limited to demographic, diagnostic and procedural information, and requires careful interpretation.

1.7 Clinicians and healthcare professionals

We have received very few adverse incident reports from the clinical community. Advice and guidance issued by the professional clinical colleges and associations is supportive of the continued use of vaginal mesh implants for surgical treatment of SUI, whilst reemphasising that any surgical operation carries some risk. The clinical community is supportive of the importance of following NICE guidance when using vaginal mesh implants for POP.

1.8 Literature

In February 2012 MHRA commissioned a brief independent overview of published systematic reviews to identify, select, assess and summarise recent published systematic reviews related to the safety of vaginal mesh devices. The intention was to provide transparent, evidence-based information for the use of patient groups and policy makers.

This was followed by the 'York Report', a further commissioned report to identify key messages for each of the outcomes of interest from available research literature that had been published up to the end of 2011. This report was published in November 2012 as 'Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse'. The findings show no specific conclusions regarding the actual adverse event rates and subjective cure rates from the available literature for specific procedures. MHRA is not aware of any significant peer reviewed articles published since then.

We expect that the European SCENIHR review will take a further review of the most recent literature available and that this will complement the work commissioned by MHRA in 2012.

1.9 Evidence from other European competent authorities (CA)

There has been little evidence from other European CAs of problems or issues with vaginal mesh implants. Vaginal mesh implants were first discussed, in April 2012, at one of the regular monthly medical device vigilance teleconferences held with other European CAs. To our current knowledge, no European country has taken legal action to remove any vaginal mesh implant from the market.

The consensus opinion across other CAs in Europe is wholly in line with our current view.

1.10 Evidence from other worldwide regulators

Vaginal mesh implants remain approved for use by medical device regulators globally. MHRA has contacts with the US FDA and the Australian Therapeutic Goods Administration (TGA) and has monitored actions and statements and guidance issued by other CAs on vaginal mesh implants. The US has produced several notifications and guidance on vaginal mesh implants. Significantly, the FDA stated in July 2011 that problems with vaginal mesh implants for POP are not rare. Subsequently, in September 2011 their Obstetrics and Gynaecology Devices Panel also recommended that POP mesh implants be reclassified from class II to class III. This has generated many queries from UK based patient support groups asking MHRA to make a similar statement. However, we have not had robust evidence that this is the case, and would not normally use such a subjective term in any guidance that we might issue.

The FDA proposal, in April 2014, to reclassify vaginal mesh implants for POP from Class II to Class III would be a change for the US, but the US classification system for medical devices is not equivalent to the EU classification system. Changing the classification in the EU would likely have no equivalent effect because in the UK and EU vaginal mesh implants are already treated in the medium to high risk category.

The TGA has also recently announced that it will also be reassessing the clinical evidence for each individual mesh implant to determine if they comply with the Essential Principles which set out the requirements for safety and performance necessary for inclusion on the Australian Register of Therapeutic Goods (ARTG).

1.11 Guidance available to patients on vaginal mesh implants

In addition to any information from their GP or surgeon, there are various sources of guidance available to patients who are considering surgery for vaginal mesh implants. These include information on the NHS Choices website, NICE guidelines for patients and Patient Information Leaflets from professional clinical associations such as BAUS and BSUG. Some manufacturers also provide patient focussed information, such as leaflets or information on their website.

MHRA has webpages specifically for patients; however, these are due to be transferred over the NHS Choices webpages.

1.12 Guidance for clinicians on using vaginal mesh implants

The first source of information for a clinician considering implanting vaginal mesh implant would be the manufacturer's instructions for use (IFU) and any necessary training.

There are also various sources of guidance available to clinicians involved in surgery for vaginal mesh implants on what precautions to take, appropriate patient selection and expected complication rates.

There are NICE clinical guidelines on urinary incontinence (2013) that endorses the use of vaginal mesh implants for SUI by suitably trained surgeons, provided that more conservative treatments, such as lifestyle advice on diet and physiotherapy for training the pelvic floor muscles, have been tried first and failed.

NICE guidance published in 2009 advises that vaginal mesh implantation procedures for POP should only be used by surgeons specialising in the management of this condition, and (for some variants of the procedure) only under special arrangements for clinical governance.

1.13 Legal action in the UK and worldwide

MHRA is aware of various law suits taken by individuals against manufacturers, mainly through monitoring of press and media reports, and some which have been brought to our attention by patient support groups.

1.14 Media activity

As part of MHRA's monitoring of media activity involving medical devices, all report sources are considered to help build up a picture of issues being discussed on the safety and performance of vaginal mesh implants.

MHRA also endeavours to have an understanding of how this issue has been reported by international media sources. This allows us to have a broad appreciation of how international patients, health professionals and worldwide governments are responding to this device area.

Where necessary we have engaged with the media by providing extensive briefings to journalists.

1.15 Other related projects and research

MHRA is currently leading on various activities to improve the reporting of adverse incidents to MHRA, providing feedback to reporters, and making improvements to how we source and use clinical advice.

MHRA is aware of a number of ongoing projects being undertaken by the NHS and other clinical bodies specifically related to improving outcomes for patients from vaginal mesh implant surgery.

Also, we are aware of a number of ongoing research projects that are likely to provide useful information about the long-term safety and effectiveness of vaginal mesh implants.

2 MHRA's role and medical devices regulations

Key points

- manufacturers are responsible for ensuring that their devices are safe and fit for their intended purpose
- all vaginal mesh implants being placed on the EU market must have a CE mark which indicates that the manufacturer is declaring that the product conforms with the relevant essential requirements set out in the relevant Medical Device Directive (MDD)
- apart from the very lowest risk products, medical devices are certified by independent conformity assessment organisations called notified bodies
- the majority of vaginal mesh implants are medium risk medical devices, with some being high risk and are certified by notified bodies
- manufacturers may select any designated notified body in Europe
- manufacturers are required to have a system for reviewing post-market safety data. This system is assessed by notified bodies
- MHRA is the competent authority (CA) responsible for ensuring that all medical devices placed on the UK market are compliant with the Medical Device Regulations (MDR) and has a duty to enforce this legislation on behalf of the Secretary of State for Health. MHRA operates a system of device vigilance and will take appropriate action should safety issues arise.
- CAs designate and monitor the performance of notified bodies within their own countries
- CAs do not routinely review or hold technical/clinical/safety data for medical devices, but they will work in partnership with notified bodies to ensure that manufacturers are compliant with the legislation
- all adverse incident reports and vigilance reports to MHRA are recorded on our database and are assessed to determine whether there is a need for further corrective action
- NHS Scotland has its own adverse incident centre for investigating incidents occurring in Scotland. However, any action to remove a device from the market in Scotland would have to be taken by MHRA, as the UK CA
- CAs have well developed systems in place for collaboration and information sharing about the post-market safety of medical devices
- the current European Union Medical Devices Directives are expected to be replaced with new regulations in 2018.

2.1 Medical device regulations

2.1.1 The current legislation

All medical devices that are placed on the market in the UK have to comply with two sets of device-specific legislation:

- EU laws – the Medical Devices Directives and Regulations
- UK laws – the Medical Devices Regulations (these transpose the EU legislation and do not set out any additional requirements above and beyond those in the EU legislation).

The legislation places obligations on manufacturers to ensure that their devices are safe and fit for their intended purpose before they can be CE marked and placed on the market in any EU member state. Manufacturers have to declare conformity with the regulations and need to demonstrate that their

devices meet essential requirements, including biocompatibility, toxicity, technical specifications, clinical data, sterilisation, right through to packaging and labelling. Manufacturers must also ensure that any declared benefits of their devices outweigh the risks.

MHRA is responsible for ensuring that all medical devices placed on the UK market are compliant with the relevant legislation and has a duty to enforce this legislation on behalf of the Secretary of State for Health. MHRA investigates all allegations of non-compliance, has responsibilities for monitoring safety of devices in the market place and ensures that the appropriate action is taken whenever necessary to prohibit or restrict unsafe products being placed or kept on the market and/or put into service.

In the event that a breach of the legislation is identified, any enforcement action taken by MHRA will be proportionate and risk based. Action may range from prosecution where there is a serious risk to public health, or for repeated non-compliance, to other forms of less noticeable compliance action where the product may remain on the market pending the corrective action. MHRA can also enforce suspension notices and prohibition notices to restrict, suspend or stop the supply of any devices which are considered to be unsafe or not in compliance with the regulations.

The EU has a process that allows individual Competent Authorities (CA) to share details of identified compliance issues with other member states. This communication is shared on the understanding that information will be kept confidential, in accordance with EU legislation.

MHRA has not carried out any enforcement action related to vaginal mesh implants and has not been made aware of any other CA doing so at the present time, within the EU. Although it is feasible that a Member State may not share information regarding a particular enforcement action with other Member States; MHRA understands that this would be a rare situation, given the fact that the products, once CE marked, can be placed across the EU without further restrictions.

Aside from information from the vigilance reporting system, we do not generally hold information on the safety data or technical files for individual devices – this information is held by the manufacturer. Manufacturers are, however, expected to provide any of this information to CAs if requested, which we have done so for vaginal mesh implants (see Section 4.7.5). We also do not generally hold information on how many types of devices are on the market, how many have been implanted and where implantation procedures have taken place.

2.1.2 The CE mark

The CE mark that appears on a medical device or on its packaging indicates that the manufacturer is declaring that the product conforms with the relevant essential requirements in the relevant Medical Device Directive (MDD) and is fit for its intended purpose as specified by the manufacturer. All vaginal mesh implants being placed on the EU market must have a CE mark.

A medical device with a CE mark indicates that the manufacturer has made a 'declaration of conformity' that their product meets the relevant essential requirements that apply. This would include demonstrating that the following are satisfactory:

- the benefits outweigh any risks
- clinical evaluation
- biological/toxicological safety data
- sterilization validation data.

2.1.3 Notified bodies

Apart from the very lowest risk products, medical devices are certified by independent conformity assessment organisations called notified bodies. MHRA is the CA in the UK that oversees UK notified bodies.

Our role includes: designating UK notified bodies; ensuring that a notified body is suitably qualified to perform all the functions that it has been designated for, conducting regular audits of the notified body's

quality assurance processes, monitoring their certification and sample witnessing of notified body audits of manufacturers to ensure that they operate to high standards.

There are about 60 notified bodies designated across Europe that manufacturers may use, with five in the UK.

In September 2013, the European Commission (EC), under the current MDD, introduced a process of joint audit of notified bodies by multinational teams, replacing the previous system that left responsibility for the oversight of notified bodies solely to the competent authority of the Member State in which the notified body was based. This was introduced as a measure to ensure that all notified bodies were managed to harmonised standards across the EU.

2.1.4 Benefit risk assessment by manufacturers

The first step for the manufacturer of a medical device is to follow the guidance set out by the EC guidance on clinical evaluation. This involves an analysis of the benefits and risks – a review of the intended benefits, potential harms and the potential sources of harm. Once the harms and sources have been identified, then they can be assessed to evaluate the risks – are the risks as low as reasonably practical? Once all mitigating factors are in place, are the residual risks acceptable?

Manufacturers are required to make judgments relating to safety of their medical devices. This includes the acceptability of risks, taking into account the generally accepted state of the art, in order to determine its suitability to be placed on the market for its intended use. Before the medical device is placed on the market for clinical use, the manufacturer should ensure that the medical benefits of the intended use of the vaginal mesh implant outweigh the risk.

Manufacturers are also required to undertake post-market surveillance activities to review experience on their devices in use and then implement any necessary corrective actions as a result of their review. Such safety corrective actions will need to be notified to CAs and to device users through a Field Safety Notice.

Manufacturer should review risk–benefit analysis in light of data gathered in the post-market phase

2.1.5 Benefit risk assessment by notified bodies

Pre-market phase

Prior to issuing a safety CE certificate, a notified body will carry out an audit of the manufacturer's full quality assurance system in accordance to the internationally agreed standard on quality assurance for medical devices (ISO 13485) and the requirements of the relevant conformity annex of the Directive. In addition for class IIb devices such as vaginal mesh implants, the notified body will sample full technical files from across the range of products to ensure that the requirements of the MDD are being met.

The review of the technical file covers as a minimum:

- the intended use of the device
- the validity of the essential requirements checklist
- a review of the risk management file (which would comprise a thorough review of the clinical evaluation report and the risk–benefit analysis)
- pre-clinical data (studies in animal models, biocompatibility, technical performance tests etc)
- clinical evaluation in accordance with Annex X of the MDD (93/42/EEC)
- information supplied by the manufacturer in the labelling and instructions
- other technical documentation based on risk.

The sampling regimen for technical files is set out by the European Operations Group for notified bodies. At least one product from each device group will be reviewed on a three year cycle.

Post-market phase

Notified bodies are also required to review the appropriateness of the manufacturer's post-market surveillance system.

In addition, the notified body is required to be provided with vigilance reports from the manufacturer when they are submitted to the relevant CA. These are reviewed to determine any significant or recurring issues. Where significant or recurring issues are noted, this could lead to an unannounced audit at the manufacturer's premises. During audits of notified bodies, the CA will review the systems and processes in place to review and monitor vigilance reports. Examples of reports received will be reviewed and any action taken followed through.

On certificate renewal and at onsite audits, the notified body will follow up on post-market data to ensure this is being collected and that the manufacturer's procedures relating to risk are still in line with the requirements. Technical files will continue to be reviewed in accordance to the sampling regime described above.

Following the initial review subsequent reviews by the notified body would also focus on the continued risk–benefit analysis when reviewing the technical file based on experience and data gained during the life of the product.

In accordance with recently issued EU guidance, notified bodies are now required to conduct unannounced inspections. The requirement stipulates that these must occur at least every three years. However, these can be brought forward if the device in question is frequently non-compliant or if specific information provides reasons to suspect non-conformities of the devices or of their manufacturer. An example could be a high number of vigilance reports with a pattern for a recurrent issue.

2.1.6 Medical device classification

There is a vast range of medical devices available: from first-aid bandages to MRI scanners and heart valves. Therefore, not all medical devices will undergo the same level of the assessment before being awarded a CE mark. Medical devices are classified according to the degree of inherent risk associated with them and the assessment they undergo before being awarded a CE mark, will reflect this classification.

Vaginal mesh implants are generally classified as medium risk – Class IIb, with some biological meshes being classified as high risk – Class III, as they have an absorbable component. The assessment they undergo before being awarded a CE mark will be in line with their classification.

2.1.7 Clinical evidence

Whatever the risk classification of the device, manufacturers are required to have clinical data to support the claims in relation to the device. This can be based on literature of equivalent devices. Devices in the highest risk category are expected to have been the subject of a clinical trial (clinical investigation).

Clinical evaluation of a medical device is required when demonstrating conformity with relevant essential requirements to verify the clinical safety and performance. For medical device implants, this process is particularly important, as the technical and biological characteristics of a device when implanted in the body need to be understood and documented.

A large number of implants, including vaginal mesh implants, placed on the market do not have any new clinical investigations undertaken. However, as part of their post-market surveillance (PMS)

activities, manufacturers should be gathering clinical data on devices already in use, not only to ensure the safety of those devices, but also to inform the development and clinical evaluation of future devices.

Notified bodies will assess the clinical evaluation made by manufacturers as part of the conformity assessment, ensuring that appropriate clinical investigations have taken place. For higher risk devices, notified bodies will assess the documentation for the medical device. All of the vaginal mesh implants are CE marked, and the majority are Class IIb medical devices which means a notified body will have sampled across the range of a manufacturer's products and processes to ensure that the essential requirements of the Medical Device Directive are being met. The manufacturer's technical files will also be sampled which will include a review of the risk management file.

2.1.8 Vigilance reporting

Manufacturers are legally responsible, via the various Annexes of the MDD, to operate a post-market surveillance (PMS) system about device performance and safety; this specifically includes vigilance reporting as a minimum. Manufacturers are obliged to submit vigilance reports to CAs using the information that they collect – usually from the clinical community, but clearly they can only report on issues of which they are made aware via their PMS systems.

MEDDEV guidance documents are available that promote a common approach by manufacturers, notified bodies and CAs to ensure uniform application of the MDD. [MEDDEV 2.12-1 rev 8](#), provides guidelines on a medical devices vigilance system and outlines the criteria required for incidents to be reported by manufacturers to CAs. For an incident to be considered to be reportable under vigilance, it must meet all of the following:

- an event has occurred – this also includes situations where testing performed on the device, examination of the information supplied with the device or any scientific information indicates some factor that could lead or has led to an event
- the manufacturer's device is suspected to be a contributory cause of the incident
- the event led, or might have led, to one of the following outcomes: (i) death of a patient, user or other person (ii) serious deterioration in the state of health of a patient, user or other person.

MEDDEV 2.12-1 rev 8 also indicates when an event is not ordinarily considered to be reportable under vigilance. Listed among these conditions include expected and foreseeable side effects which must meet all of the following criteria:

- clearly identified in the manufacturer's labelling
- clinically well known as being foreseeable and having a certain qualitative and quantitative predictability when the device is used and performs as intended
- documented in the device master record, with an appropriate risk assessment, prior to the occurrence of the incident and
- clinically acceptable in terms of the individual patient benefit.

Notified bodies have a responsibility for ensuring that manufacturers can and do operate a suitable PMS system.

MHRA is responsible for collecting vigilance data and evaluating it centrally (Article 10 of the MDD). We do this for the UK and we share information with others in the EU in accordance with the Directives and EU guidance. We have collated the EU vigilance experience which does not suggest any safety signals for vaginal mesh implants (see Section 4.8). If we believe that a manufacturer is not operating a suitable PMS system we would approach them first and the relevant notified body concerned, along with their designating CA.

2.1.9 Post-market surveillance (PMS)

The MDD require manufacturers to undertake PMS. MHRA expects notified bodies to assess the appropriateness of a manufacturer's PMS system as part of their assessment. MHRA also monitor some aspects of the effectiveness of manufacturers systems through the vigilance system.

2.2 MHRA's role and responsibilities

2.2.1 Role and regulatory responsibilities

MHRA acts as the CA for the UK and is responsible for regulating all medicines and medical devices by ensuring they work and are acceptably safe. Underpinning all our work lies robust and fact-based judgements to ensure that the benefits justify any risks.

We are responsible for a number of specific functions including:

- the designation and monitoring of UK notified bodies
- reviewing applications for Clinical Investigations which will be carried out in the UK
- adverse incident investigation
- registration of in-vitro diagnostic and low risk medical devices
- market surveillance
- compliance, investigation and enforcement.

MHRA is responsible for market surveillance including the receipt of adverse incidents and other safety information, and can take appropriate action to restrict the use of devices (see Section 2.1.1).

Adverse incident investigation

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

Whilst there are regulatory obligations for manufacturers to report and investigate all adverse incidents involving medical devices to the MHRA (see Section 2.1.8 vigilance reporting), it is not compulsory for clinicians to do so. However, GMC guidance published in February 2013 makes it clear that clinicians should report medical device adverse incidents to MHRA, and make information available to patients about how they can report adverse events to us. In addition, MHRA actively encourages voluntary reporting of adverse incidents involving medical devices from clinicians, hospitals, other healthcare professionals and members of the public.

All adverse incident reports and vigilance reports to MHRA are recorded on our Adverse Incident Tracking System (AITS) database. Every voluntary adverse incident reported to MHRA is routinely passed on to the manufacturer- if known – for their further investigation and to contribute to their PMS, which is required under the regulations (see Section 2.1.7). Personal details of patients and members of the public are only passed on to the manufacturer if they have given consent for this. If these reports are subsequently determined to be vigilance reportable under the regulations, then the manufacturer has to inform MHRA and carry out an investigation as appropriate. The manufacturer will provide MHRA with a report with their conclusion and root cause analysis.

For some adverse incident reports, which are initially assessed by MHRA as serious, we are more actively involved in the manufacturer's investigation, monitoring and directing their progress and meeting with them if necessary.

2.2.2 MHRA's wider public health role

When assessing an adverse incident report that has been submitted to MHRA, several factors are considered to account for the acceptability of the risk associated with the event.

These include:

- causality
- technical/other cause
- probability of occurrence of the problem
- frequency/scale of use
- detectability
- probability of occurrence of harm
- severity of harm
- manufacturers stated intended purpose of the device.

MHRA will then determine the adequacy of the actions taken, or proposed actions by the manufacturer, and whether there is a need for further corrective action. Further action may include:

- gathering more information (for example by commissioning independent reports)
- making recommendations to manufacturers, such as updating the instructions for use (IFU) for the medical device or making changes to the manufacturer's quality systems
- monitoring the effectiveness of manufacturer's field safety corrective actions, examples of which are: sending out a Field Safety Notice of a product recall; repair of a device in situ; issuing advice on restriction of use
- having discussions with the relevant notified body on matters related to the certification of the device involved in the adverse event
- taking appropriate regulatory action, where necessary, including withdrawal of product.

Many of the issues that arise in relation to devices safety are concerned, not simply with the characteristics of the products themselves, but the interface between the product and the manner in which they are used.

MHRA has an important role in working with healthcare professionals and the public, not only to inform, but also to influence behaviour. Therefore, other actions we take may include:

- issuing specific advice to the health service through Medical Device Alerts and also, more generally, through safety pamphlets, posters and bulletins
- provide recommendations and facilitating further education or training of professional users
- liaising with professional bodies where there may be implications for education, training or other aspects of clinical practice.

We will also endeavour to ensure that:

- other CAs are kept informed
- the European Commission is kept informed and consulted where necessary (for example, if it is considered that re-classification of the device may be required).

The decision to issue a Medical Device Alert involves assessment and review by medical device specialists, Devices Clinical team and senior MHRA staff. For vaginal mesh implants, no Medical

Device Alert has been issued to date, as we do not consider we have any new information or guidance to bring to the attention of clinicians that was not already available to them. However, close collaboration with the DH, NHS England and professional clinical associations resulted in a letter to NHS Medical Directors in November 2012 on Vaginal Tapes and Meshes (see Annex A). This letter from Sir Bruce Keogh and Professor Keith Willet, highlighted the publication of MHRA's 'York Report' (see Section 4.4.2) and action agreed by DH, the then NHS Commissioning Board, MHRA and the relevant professional associations to reduce the rates of adverse events with these devices. It also asked them to ensure familiarity with existing NICE and professional guidance on the safe and appropriate use of these devices.

In December 2013 a further letter was issued to NHS Medical Directors from Professor Bruce Keogh and co-signed by relevant clinical associations on the surgical management of urinary incontinence and pelvic organ prolapse (see Annex B). This stated that NICE guidance should be followed and that of particular relevance, important issues were: patient consent, audit, adverse event reporting to MHRA and specialist care arrangements for surgery for mesh removal.

MHRA continuously assesses and reviews any new information and may consider the option of a Medical Device Alert in the future, if considered appropriate.

2.2.3 How the regulations apply in Scotland – and other devolved administrations

NHS Scotland has its own adverse incident centre for investigating incidents occurring in Scotland. This centre works closely with MHRA and routinely informs us about the occurrence of all incidents and any conclusions reached. This process ensures that MHRA has information on all adverse incidents occurring in the UK, for which it is legally responsible. Thus Scotland is an important contributor and partner in assessing reported post-market experience with medical devices.

MHRA assesses manufacturer's field safety corrective actions on behalf of the UK and informs the Scottish Government in advance when it is considering issuing supplementary safety warnings over and above the manufacturer's actions. If this happens, Medical Device Alerts are issued by the MHRA for action in England and are sent to the devolved administrations who have their own contact details within the alert.

Whether or not a particular medical device is chosen to be used within NHS Scotland is a decision for their NHS Boards, individual clinicians and their patients to consider, taking account of risks and benefits. NHS Scotland is, therefore, able to advise their institutions and clinicians not to use a particular device if they believe that this is the correct course of action for them. It would not be a decision linked to the UK Medical Devices Regulation.

Any decision or guidance that advises against the use of a medical device on safety grounds would need to be considered carefully with reference to all available evidence, and it would naturally raise questions for MHRA, the other devolved administrations, and the rest of Europe. The positive benefits for many patients would have to be considered.

Any action to remove a device from the market in Scotland would have to be taken by MHRA who have the delegated enforcement authority for the Medical Devices Regulations for the whole of the UK and whose enforcement powers are contained in the Consumer Protection Act 1987.

2.3 Working in Europe

European CAs have well developed systems in place for collaboration and information sharing about the post-market safety of medical devices and, where appropriate MHRA is a proactive participant in these activities.

2.3.1 Medical device expert group – vigilance

The European Medical Device Expert Group has had an active vigilance sub-group for many years. The group meets two to three times each year to discuss strategic issues relating to medical device vigilance reporting and it has developed comprehensive systems for information sharing amongst member states and detailed guidance for manufacturers on requirements for vigilance reporting.

2.3.2 Vigilance telephone conferences

Since mid-2012, the European Commission has coordinated monthly telephone conferences to discuss both emerging and ongoing medical device vigilance issues. All member states are encouraged to participate, with more than 20 member states routinely taking part each month. These meetings have considerably improved collaboration on vigilance related activities and have resulted in the establishment of a number of task forces (typically involving from three to five CAs) to coordinate activities on specific safety issues. The safety of vaginal mesh implants has been a standing agenda item since mid-2013 so that member states have the opportunity to share any new information. A task force on vaginal mesh implants was set up in April 2013 to establish a mandate of work for the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR).

2.3.3 National competent authority reports

Member states exchange information about the outcomes of medical device safety investigations, recalls within the EU and other regulatory actions by European CAs using the National Competent Authority Report (NCAR) system, which is overseen by the European Medical Device Expert Group. Over the period January to July 2014 (7 months) 629 medical device NCARs were circulated by member states, of which 148 originated from MHRA, with none related to vaginal mesh implants.

2.3.4 SCENIHR

In March 2014, the European Commission, based on the work of the vaginal mesh implant task force (see Section 2.3.2), requested SCENIHR to deliver an opinion on the safety of surgical meshes used in urogynecological surgery. The committee is made up of experts from a number of member states. It deals with questions concerning emerging, or newly identified, health and environmental risks and broad, complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health. It also addresses related issues not covered by other Community risk assessment bodies. SCENIHR is expected to publish its preliminary opinion on surgical meshes in early 2015.

All experts participating in the Scientific Risk Assessment Advisory Structure need to declare commitment, confidentiality, and interests in the subject matter before participating in the work. Declarations of interests are updated orally at each meeting. The declarations will be published once the work on the particular subject matter has been concluded. Likewise, the composition of a Working Group is published only once an opinion has been approved by the [Scientific Committee](#).

2.4 Revision of the Medical Devices Directives

2.4.1 Introduction

On 26 September 2012, the European Commission published proposals for two new regulations on medical devices and in-vitro diagnostic devices (IVDs), which will replace the existing three directives regulating medical devices in the European Union (EU).

The original European legislation on medical devices was drafted over 20 years ago and since then there has been substantial changes in medical device technology and the number of Member States in the EU has more than doubled.

As a consequence, the application of the existing medical devices directives has been inconsistent across the EU. This makes it difficult for the legislation to achieve its objectives: ensuring the safety of medical devices and their free movement in the EU's single market.

Moreover, it is imperative to learn lessons from recent events that have raised questions about the regulatory framework, including those involving the safety concerns of some metal-on-metal hip replacements and fraudulent PIP breast implants.

MHRA has engaged with the Commission to influence its proposals as they have been developed.

The main features of the regulations that have been proposed include:

- increasing transparency
- increasing requirements on traceability in the supply chain
- tightening up the designation and audit of notified bodies, which assess the safety of devices before they are placed on the market
- subjecting higher risk devices to additional pre-market scrutiny
- requiring more clinical evidence for higher risk and implantable devices
- introducing reporting of serious incidents and field safety corrective actions to a new central EU database
- improving coordination between Member States
- establishing a new governance structure of Member State experts and centralised clinical expertise; and
- aligning with the EU's recently updated New Legislative Framework for the internal market.

MHRA expects that new legislation will be in place in 2018 and from then all products on the market in the UK will need to comply with the new rules. However, these new rules will not be applied retrospectively, therefore existing products will not need to be updated to meet the new requirements.

2.4.2 Traceability and unique device identifiers (UDIs)

One of the major innovations of both of the proposed regulations is to establish a system of unique device identification (UDI). These precise codes placed on every medical device by the manufacturer, linked to a database that holds detailed information on all devices.

UDI will facilitate the identification and traceability of devices. Economic operators and health institutions will be obliged to maintain electronic records of UDIs and manufacturers will be required to refer to the UDI in their technical documentation and when reporting serious incidents and undertaking field safety corrective actions. Implementation of the UDI system will be proportionate and risk-based.

The proposed regulations for medical devices will require manufacturers of implantable devices to provide an implant card for patients. The regulation sets out what information needs to be included on the card: the UDI code, any relevant warnings, the expected lifetime of the device and any follow-up of which the patient should be aware. This information must be in plain language.

In principle, MHRA supports this new requirement. It became clear during the events involving fraudulent PIP breast implants that many patients did not know the manufacturer of their breast implants. Implant cards will improve traceability and patients' awareness. However, we are keen to ensure that any requirement for implant cards takes account of existing practice within the NHS so that information can be provided to patients in a way that they find most useful – electronically, for example.

Some manufacturers already use coding systems, such as GS1, which are likely to form the basis for the future European UDI system. MHRA recognises the value of UDIs in helping to monitor the safety and performance of implantable medical devices. We will be working with the Department of Health,

NHS organisations, the Health and Social Care Information Centre and the Clinical Practice Research Datalink (CPRD) to encourage NHS trusts to implement systems for UDI recording and analysis. This is currently being piloted in a couple of hospitals to apply to all implantable devices – which would include vaginal mesh implants if used at these hospitals.

2.4.3 Notified bodies

The proposed regulations detail clearer requirements for CAs, such as MHRA, who are responsible for designating notified bodies:

- there will be a joint assessment process, including representatives of the Commission and other Member States, before CAs designate organisations as notified bodies - a very similar process to that put in place recently under existing legislation
- all existing notified bodies will need to be re-designated under this new process.
- the authorities must explain to the Commission and other Member States how they oversee notified bodies
- each CA must be peer reviewed by another authority every second year and peer review another authority in-between; this process is organised by the Member States.

The regulations also require a lot more detail about individual notified bodies. This includes: their legal status and organisation structure, quality management system, process requirements, and more detailed resource requirements. For example, notified bodies will have to employ personnel with clinical expertise in order to challenge scientifically the clinical data presented by a manufacturer and make an objective clinical judgement about the assessment of the manufacturer's clinical evaluation.

In addition, notified bodies must have clear oversight and responsibility for any subcontracted work or subsidiaries.

Tightening up the monitoring of notified bodies with assessments, audits and better communication is crucial to ensure a consistent level of scrutiny of manufacturers and devices across the EU. However, as highlighted previously, an interim measure has been put in place to improve the safety of medical devices, meaning that all EU notified bodies will to be subject to a joint assessment and be re-designated before October 2016.

2.4.4 Clinical evidence

MHRA is of the view that there should be clearer rules on when it is appropriate for manufacturers to use clinical data sourced from studies on a similar device (termed 'equivalence').

The proposed new European legislation sets out the circumstances where equivalence may be used: the devices must have the same intended purpose and their technical and biological characteristics and the medical procedures must be so similar that there would not be a clinically significant difference between their safety and performance. In addition, the legislation carries forward the existing requirement for a manufacturer to give due justification if they do not intend to perform specific clinical investigations on a class III or implantable device.

More broadly, regardless of whether equivalence is used, manufacturers must evaluate thoroughly the relevant clinical data in order to demonstrate the safety and performance of their device.

The proposed regulation on medical devices improves this in two ways. Firstly, the regulation sets out that a manufacturer's clinical evaluation must include a critical evaluation of the relevant scientific literature, with a requirement to conduct a clinical investigation where existing clinical data are insufficient. Secondly, with oversight from Member States, the European Commission will adopt common technical specifications on specific devices, or groups of devices, which can be used to clarify the requirements on manufacturers when they conduct a clinical evaluation for certain devices or types

of device. Manufacturers will have to comply with these common technical specifications unless they can demonstrate how they have met the equivalent level of safety and performance by other means.

It is also important that manufacturers' clinical evaluations are properly assessed and the use of equivalence critically appraised by notified bodies. All of the vaginal mesh implants are CE marked, and the majority are Class IIb medical devices which means a notified body will have sampled across the range of a manufacturer's products and processes to ensure that the essential requirements of the Medical Device Directive are being met. The manufacturer's technical files will also be sampled which will include a review of the risk management file.

As the new European legislation will not come into effect until at least 2018, Member States are also taking additional voluntary action to check and improve the quality of notified bodies. MHRA has rigorously audited the notified bodies which assess the highest risk devices, including implants, in the UK and taken action to support their assessment of clinical evidence.

2.4.5 Post-market surveillance (PMS)

PMS is a key area being addressed in the revision of the Directives, and we expect that there will be provisions included that set out more clearly the responsibility of manufacturers to implement adequate and proportionate systems to collect information systematically on the performance of their devices in the post-production phase.

3 Vaginal mesh implants

Key points

- vaginal mesh implants are permanent and are not intended to be removed
- vaginal mesh implants are usually made from non-absorbable polypropylene, derived from non-absorbable sutures, entwined in a woven or knitted mesh construction
- in general, the same mesh material is used in different shapes or forms to treat the very different medical conditions of SUI and POP.

3.1 Vaginal mesh implants for stress urinary incontinence (SUI)

These are generally made from a narrow 'tape' of polypropylene mesh which is placed under the urethra like a sling or hammock to keep the urethra in the correct position. They have been on the market for about 20 years and can be implanted in a half-hour, minimally invasive surgical procedure under local anaesthetic as an out-patient.

They are permanent implants that are not intended to be removed. They are generally made from non-absorbable polypropylene, derived from non-absorbable sutures, entwined in a woven or knitted mesh construction. The pore size within the mesh varies depending on the diameter of the polypropylene yarn/filament used and the construction method for the mesh.

They are placed trans-vaginally to support the mid-urethra or bladder-neck when the pelvic floor muscles and urethral sphincter are weakened or damaged and unable to stop urine from leaking. There are a variety of different tapes available that differ in the surgical insertion technique used.

There are two main types of procedures; a retropubic approach or a transobturator approach. A vaginal mesh tape is inserted through a small (1-2 cm) cut in the vagina, to support the urethra. The surgeon then makes two smaller cuts just above the pubic area (retropubic) or on the inside of both thighs (transobturator) and passes the vaginal mesh implant through. The whole procedure takes approximately 20-30 minutes. More recently single incision approaches have been introduced whereby the tape is inserted via a single vaginal incision.

Three most common vaginal mesh implants used are:

- TVT (tension free vaginal tape) – the operation involves inserting the tape from an incision on the front wall of the vagina and then up to two small incisions on the lower abdomen. The tape supports the urethra, lying between the vaginal wall and the urethra.
- TOT (trans obturator tape) – similar to TVT but involves a different insertion technique, involving a small cut at the top of each thigh where the tape is brought out and cut off level with the skin.
- Mini-slings – these are designed to minimize the operative procedure as much as possible to reduce complications of thigh pain and bladder outlet obstruction. Introduced via a vaginal incision to the internal obturator muscle.

There is extensive information on the different tapes available and surgical techniques involved in the recently updated NICE guidance CG171 on the management of urinary incontinence in women.

3.2 Vaginal mesh implants for pelvic organ prolapse (POP)

Vaginal mesh implants used to treat POP come in various sizes and shapes. They are made of polypropylene and some products may also incorporate a biological/absorbable component, such as a coating. These vaginal mesh implants are placed in the pelvic floor area in a number of different ways to support the vaginal wall and/or other pelvic organs.

They are permanent implants that are not intended to be removed. They are generally made from non-absorbable polypropylene, derived from non-absorbable sutures, entwined in a woven or knitted mesh construction. The pore size within the mesh varies depending on the diameter of the polypropylene yarn/filament used and the construction method for the mesh. A larger area of mesh is used for POP repair than that used for treating SUI.

POP is the bulging of one or more of the pelvic organs, such as the uterus, vagina, bowel and bladder into the vagina. This usually occurs as a result of weakened pelvic floor muscles. There are three main types of POP and it is possible for a patient to have one or more types of prolapse at the same time. These include:

- anterior prolapse (cystocele), where the bladder bulges into the front wall of the vagina
- prolapse of the cervix or top of the vagina, where the cervix or uterus drops, and can be the result of previous hysterectomy
- posterior wall prolapse (rectocele or enterocele), when the bowel bulges forward into the back wall of the vagina.

The procedure for insertion of the mesh varies depending on the type and extent of prolapse being treated, and is generally performed with the patient under general anaesthesia, using an open or laparoscopic abdominal or vaginal approach.

4 Evidence and data related to safety of vaginal mesh implants

Key points

- adverse incidents reported to MHRA and National Reporting & Learning System (NRLS) give an indication of the type of common complications associated with vaginal mesh implants
- manufacturer sales figures and hospital episodes statistics (HES) give an indication of the number of implants in use, bearing in mind that HES has data for England only
- some reported accounts show that the impact of the quality of life for some patients is severe
- MHRA funded an independent review of published peer reviewed articles associated with vaginal mesh implants known as the 'York Report'
- evidence from the York Report suggests that whilst on the whole adverse events occur in only a minority of patients, the likelihood of such an event for an individual patient is not insignificant
- literature suggests that some groups of patients may be more susceptible than others in developing adverse events or that surgical expertise and experience and patient after care may play a key role in reducing adverse events
- MHRA have open communication with professional clinical colleges and associations related to vaginal mesh implants and many of these groups have issued statements supporting the use of vaginal mesh implants
- the International Urogynecological Association (IUGA) have [stated](#):
"There is robust evidence to support the use of mid-urethral slings (MUS) from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use."
- information from manufacturers was found to be consistent with that provided by a UK notified body and met with the relevant requirements for class IIb devices under current legislation
- European CAs share information regarding device issues and to the best of our knowledge, no EU country has suspended the use of vaginal mesh implants
- the FDA has issued proposals to reclassify vaginal mesh implants for POP from class II to III, but has no plans to withdraw this device for any indication
- Australia, New Zealand and Canada have reviewed the issues with vaginal mesh implants and are continuing to monitor this device area
- currently there is no national registry in the UK for vaginal mesh implants. Discussion on a national registry is ongoing between NHS England and the specialised societies and MHRA.

4.1 Evidence from adverse incident reports

4.1.1 Adverse incidents reported to MHRA

An adverse incident is an event that causes, or has the potential to cause, unexpected or unwanted effects involving the safety of device users (including patients) or other persons.

There are regulatory obligations for manufacturers to report all serious adverse incidents involving medical devices to MHRA (see Section 2.1.8 vigilance reporting). In addition, MHRA also actively encourages voluntary reporting of adverse incidents involving medical devices from clinicians, hospitals, other healthcare professionals and members of the public.

All adverse incident reports and vigilance reports to MHRA are recorded on our Adverse Incident Tracking System (AITS) database.

Every voluntary adverse incident reported to MHRA is routinely passed on to the manufacturer of the device – if known – for their further investigation and to contribute to their post-market surveillance activity, which they are required to do under the Medical Device Regulations (see Section 2.1.7).

Personal details of patients and members of the public are only passed on to the manufacturer if they have given consent for this. If the manufacturer then judges these reports to be vigilance reportable, then the manufacturer has to inform MHRA (see also Section 4.7.4 vigilance reports) and carry out an investigation as appropriate.

The following information on adverse incidents reported to us in the UK has been extracted from the AITS database for the period 2005 to 2013.

We have not provided a breakdown of adverse incident reports according to each individual manufacturer (see also 4.7.4 vigilance reports) due to Article 20 confidentiality requirements under the Medical Device Regulations. A reported adverse incident cannot necessarily be interpreted as representing a faulty device from any manufacturer.

From the limited information we have from adverse incident reports there has been no indication that any one type of adverse event is linked to a particular manufacturer, or manufacturer's model.

4.1.1.1 Incident data for vaginal mesh implants for stress urinary incontinence (SUI)

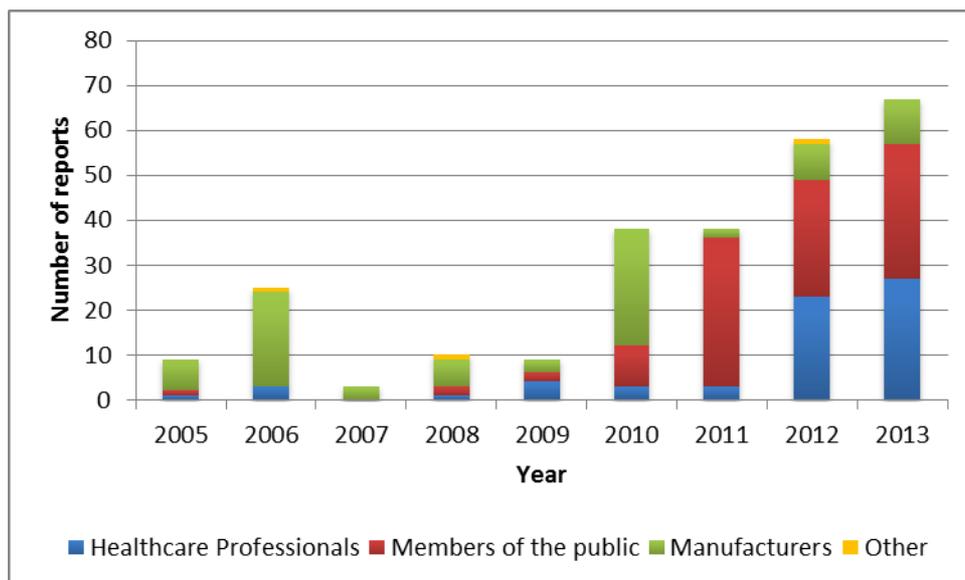
From 2005 to 2013, MHRA received a total of 291 adverse incident reports related to vaginal mesh implants used to treat SUI.

Figure 1 shows which groups have submitted these reports to MHRA, such as manufacturers, healthcare professionals and members of the public.

For voluntary reports from healthcare professionals and members of the public, Figures 2 and 3 indicate which part of the UK, they are located. However, this does not necessarily mean this is the geographical location of where the vaginal mesh device was implanted.

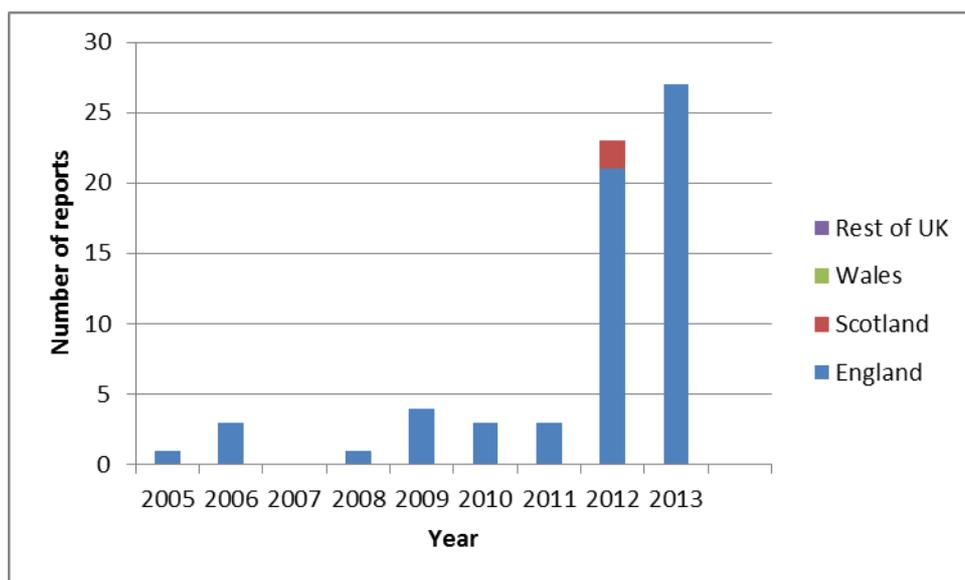
It is important to note that the number of reports submitted does not necessarily represent the same number of patients and mesh devices implanted, as some reporters have submitted separate reports for different symptoms for the same mesh implant.

Figure 1 Source of incident reports – SUI implants



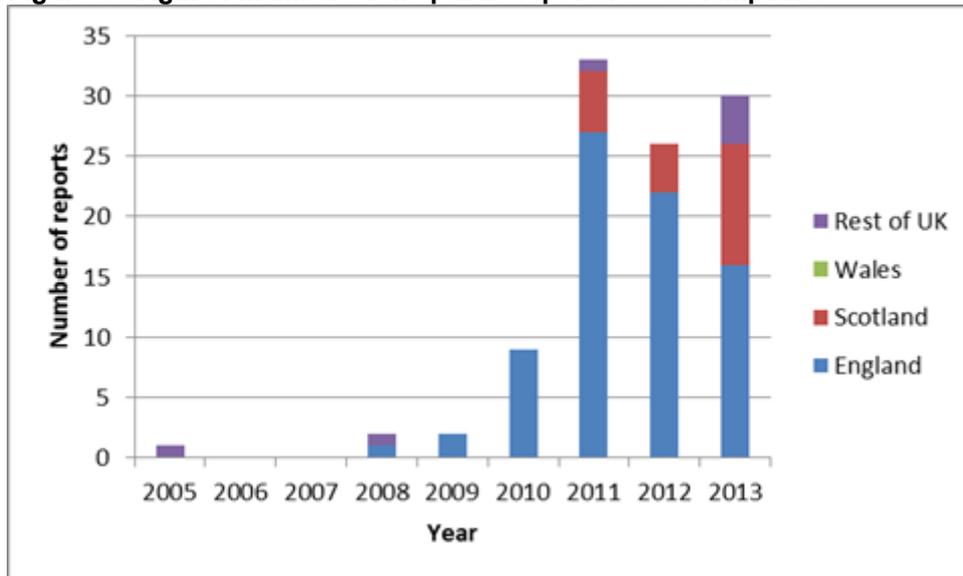
Note: Other sources refer to Devolved Administrations

Figure 2 Origin of healthcare professional reporters – SUI implants



Note: Rest of the UK refers to the rest of the United Kingdom such as Northern Ireland and Crown dependencies. It also refers to reporters who do not supply an address, but give a UK email address instead.

Figure 3 Origin of member of the public reporters – SUI implants



Note: Rest of the UK refers to the rest of the United Kingdom such as Northern Ireland and Crown dependencies. It also refers to reporters who do not supply an address, but give a UK email address instead.

The following charts provide a simplified overview of the common complications that have been reported to MHRA. The terms we have used to group the common complications are based on our interpretation of the subjective accounts within the incidents reported to us. These categories are not mutually exclusive; more than one complication may be reported in an incident report. This means that the total number of complications will add up to more than the total number of reports received.

‘pain’ – includes any reference given to post-operative pain

‘extrusion/erosion’ – refers to incidents where the mesh has either migrated or become partially exposed through vaginal tissue. It does not refer to the mesh eroding or fraying.

‘infection’ – references to post-operative infection, and for example any recurring urinary tract infection

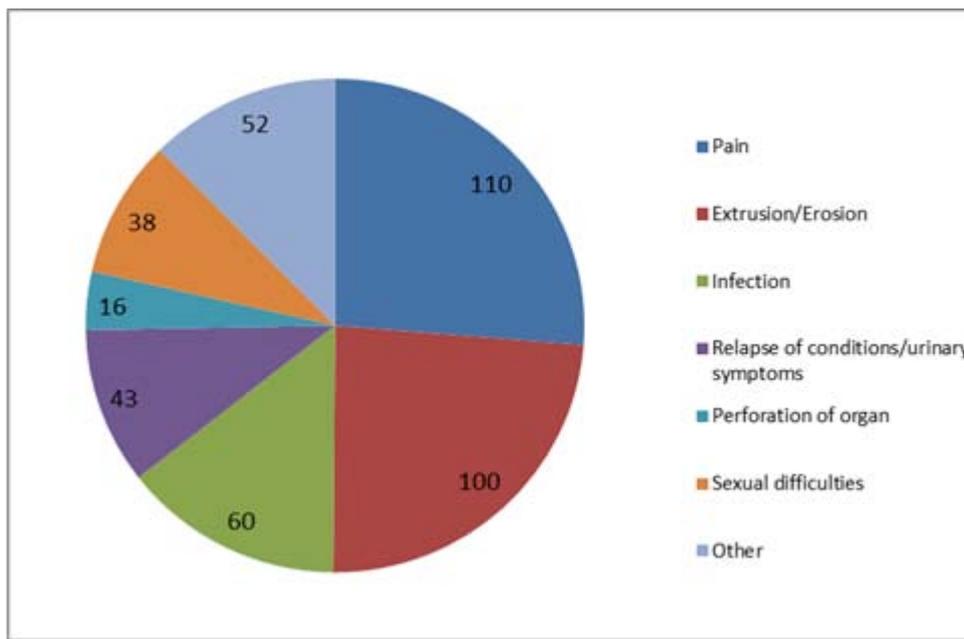
‘relapse of conditions/urinary symptoms’ – reoccurrence of urinary incontinence

‘Perforation of organ’ – refers to incidents that were procedural related, such as perforation of the bladder or bowel when inserting the mesh implant.

‘sexual difficulties’ – dyspareunia, painful sexual intercourse

Figure 4 indicates the total number of times each of the common complications has been reported from all sources, for vaginal mesh implants to treat SUI.

Figure 4 Common complications – SUI implants



‘Other’ – reported complications include:

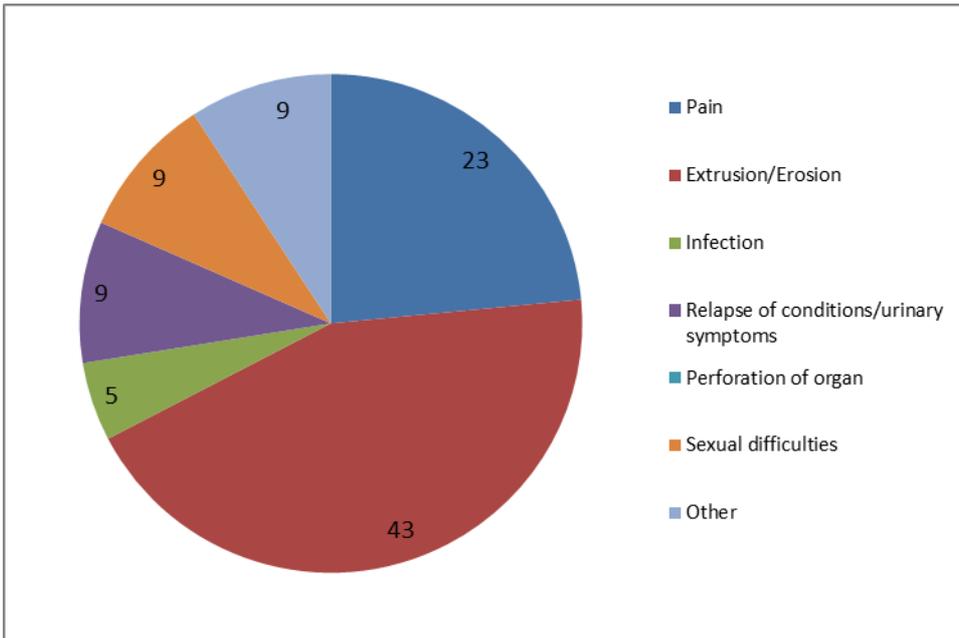
Device related	Procedural	Post procedural
<ul style="list-style-type: none"> • Packaging • Material separation 	<ul style="list-style-type: none"> • Blood loss, • Pulmonary embolism • Nerve damage • Death 	<ul style="list-style-type: none"> • Bleeding 3 months • Adverse psychological effect • Formation of stone on device • Inflammation • Fibromyalgia • blurred vision

There have been three incidents reported to MHRA where the patient died after surgery for vaginal mesh implant insertion to treat SUI. All were reported by healthcare professionals in England. For all three cases, there was agreement with the healthcare professionals who reported that the reported complications: bowel perforation and cardiac episode were consistent with complications related to the surgical procedure itself and that the mesh implant was not implicated as the cause of death.

All surgery has risks and underlying health conditions or other factors may also contribute to complications, including death.

Figures 5, 6 and 7 further break down the reported common complications as reported by healthcare professionals, members of the public and manufacturers.

Figure 5 Complications for SUI implants reported by healthcare professionals



Incidents from members of the public, indicated in Figure 6, have been recorded as reported to us. They are the patient's account of their symptoms, which in some cases, may not have been verified by their clinician as being a direct consequence of the vaginal mesh implant.

Figure 6 Complications for SUI implants reported by members of the public

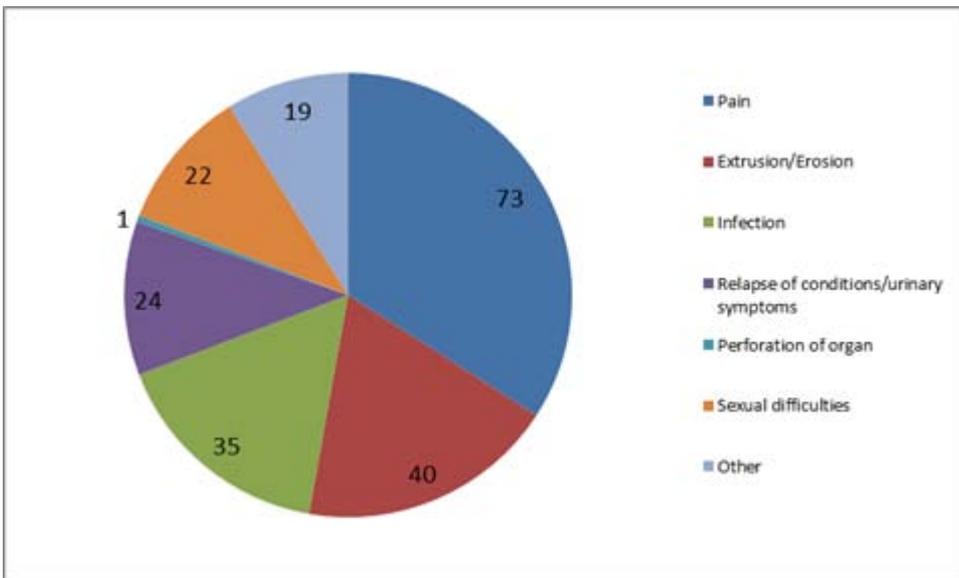
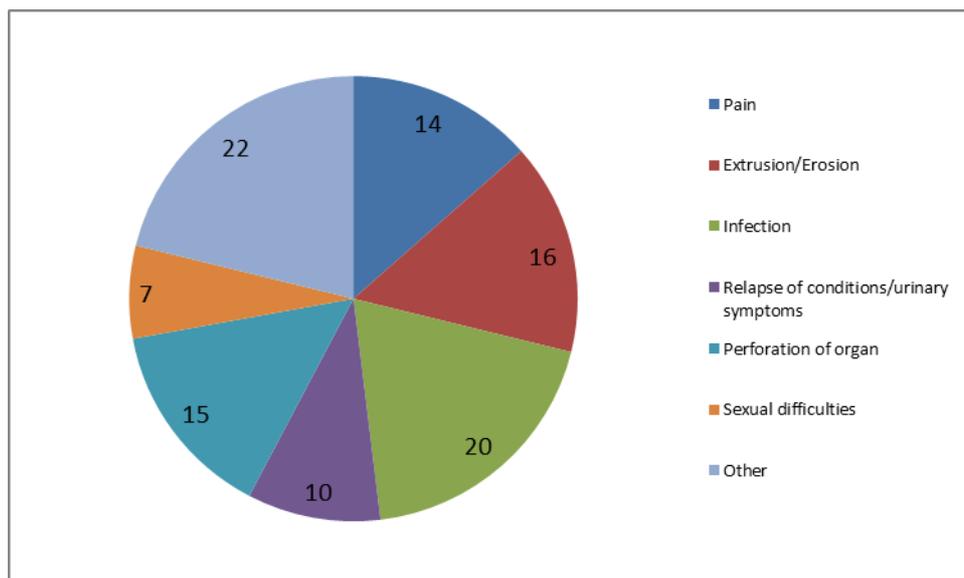


Figure 7 gives the number of incidents reported as vigilance reports. This does not include manufacturer vigilance reports for incidents we were already informed of from other voluntary sources.

Figure 7 Complications for SUI implants reported by manufacturers



4.1.1.2 Incident data for vaginal mesh implants for pelvic organ prolapse (POP)

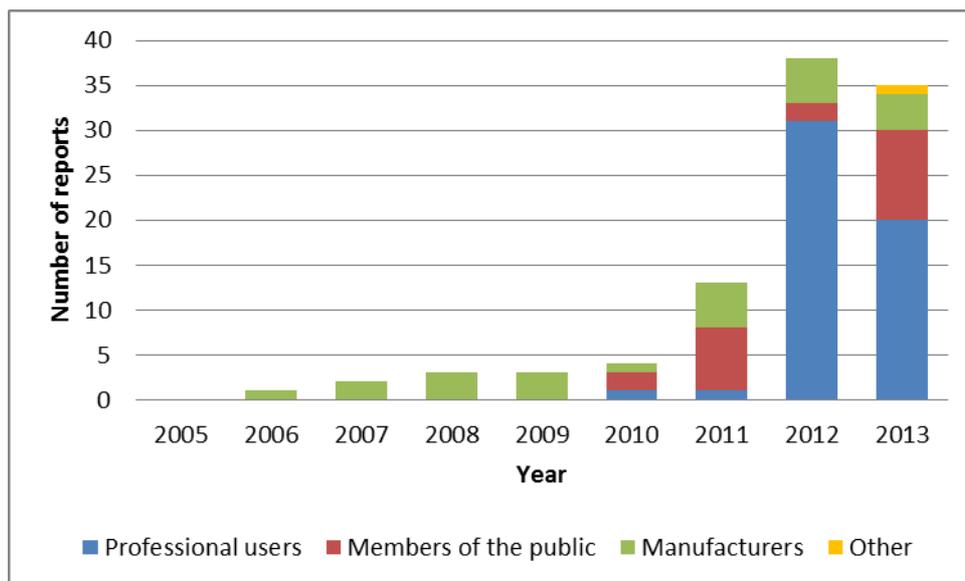
Since 2005 MHRA has received a total of 110 reports on vaginal mesh implants used to treat POP.

Figure 8 indicates which groups have submitted reports to MHRA, such as healthcare professionals and members of the public.

For voluntary reports from healthcare professionals and members of the public, Figures 9 and 10 indicate which part of the UK, they are located. However, this does not necessarily mean this is the geographical location of where the vaginal mesh device was implanted.

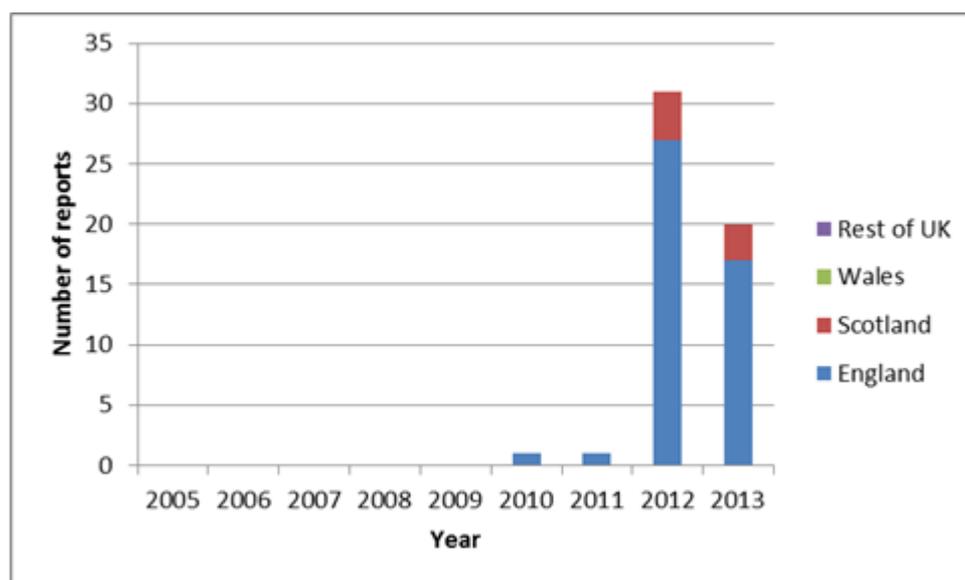
It is important to note that the number of reports submitted does not necessarily represent the numbers of adverse incidents that have occurred, as some reporters have reported different symptoms for the same ongoing issue on separate occasions.

Figure 8 Source of incident reports – POP implants



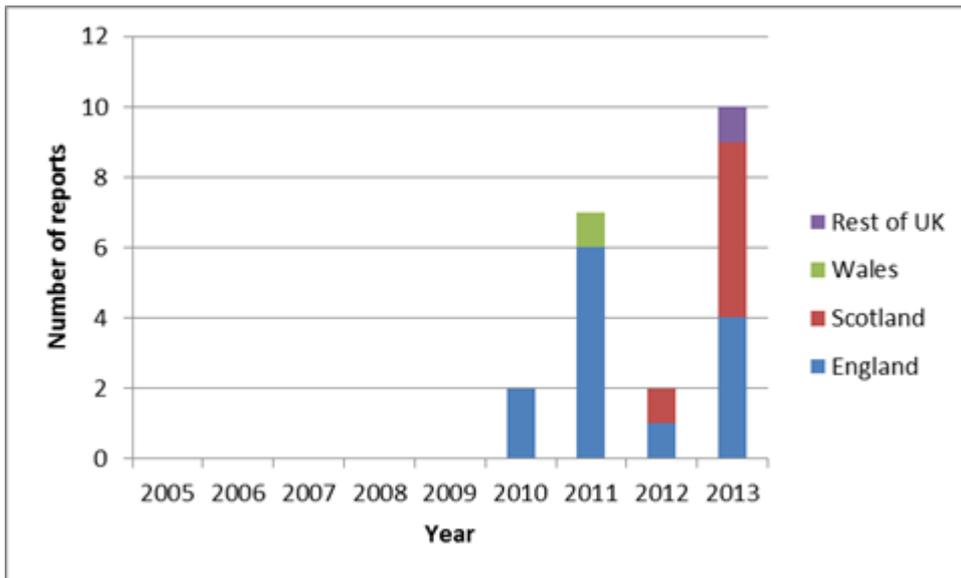
Note: Other sources refer to Devolved Administrations

Figure 9 Origin of healthcare professional reporters – POP implants



Note: Rest of the UK refers to the rest of the United Kingdom such as Northern Ireland and Crown dependencies. It also refers to reporters who do not supply an address, but give a UK email address instead.

Figure 10 Origin of member of the public reporters – POP implants



Note: Rest of the UK refers to the rest of the United Kingdom such as Northern Ireland and Crown dependencies. It also refers to reporters who do not supply an address, but give a UK email address instead.

The following charts provide a simplified overview of the common complications reported to MHRA. These categories are not mutually exclusive: more than one complication may be reported in an incident report. This means that the total number of complications will add up to more than the total number of reports received.

Figure 11 indicates the total number of times each of the common complications has been reported for vaginal mesh implants for POP. Figures 12, 13 and 14 further break down the common complications into how many times common complications have been reported by healthcare professionals, members of the public and manufacturers.

The terms we have used to group the common complications are based on our interpretation of the subjective accounts of the incidents reported to us.

‘pain’ – this includes any reference to post-operative pain

‘extrusion/erosion’ – refers to incidents where the mesh has either migrated or become partially exposed through vaginal tissue, it does not refer to the mesh eroding or fraying.

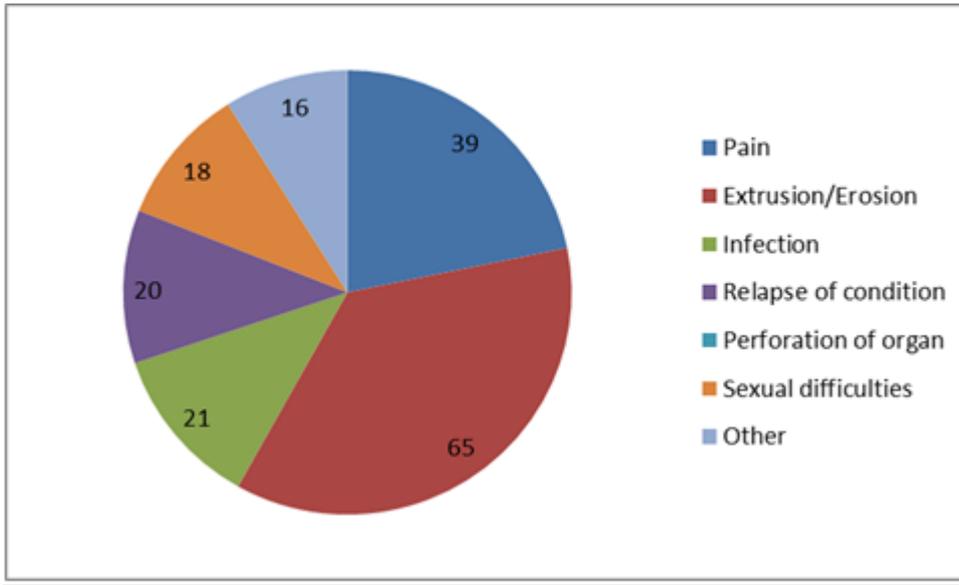
‘infection’ – references to post-operative infection, and any reference to recurring urinary tract infections

‘relapse of condition’ – further instances of prolapse

‘Perforation of organ’ – refers to incidents that were procedural related, such as perforation of the bladder or bowel.

‘sexual difficulties’ – dyspareunia, painful sexual intercourse

Figure 11 Common complications – POP implants



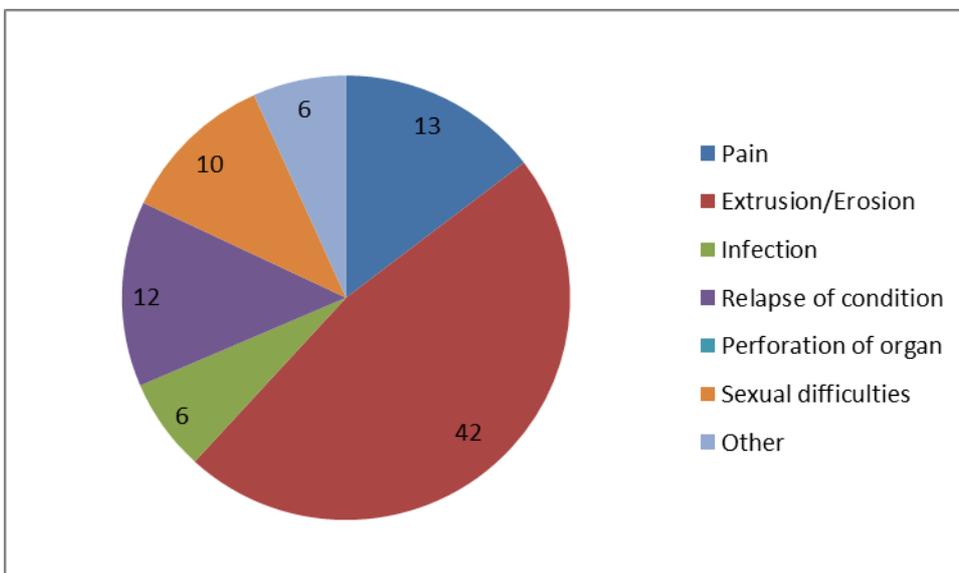
‘Other’ reported complications include:

Device related	Procedural	Post procedural
<ul style="list-style-type: none"> • Material issues • Material separation • Labelling issues • Manufacturing records non-conformance 	<ul style="list-style-type: none"> • Blood loss • Rupture of iliac artery • Death 	<ul style="list-style-type: none"> • Fistula • Thickening of vaginal skin

There was one incident reported to MHRA where the patient died after surgery reported by a healthcare professional in England. From the information we have, this was a cardiac arrest and there was agreement with the incident reporter that it was consistent with complications related to the surgical procedure itself, and the vaginal mesh implant was not implicated.

All surgery has risks and underlying health conditions or other factors may also contribute to complications, including death.

Figure 12 Complications for POP implants reported by healthcare professionals



Incidents from members of the public, indicated in Figure 13, have been recorded as reported to us. They are the patient's account of their symptoms, which in some cases may not have been verified by their clinician as being a direct consequence of the mesh implant.

Figure 13 Complications for POP implants reported by members of the public

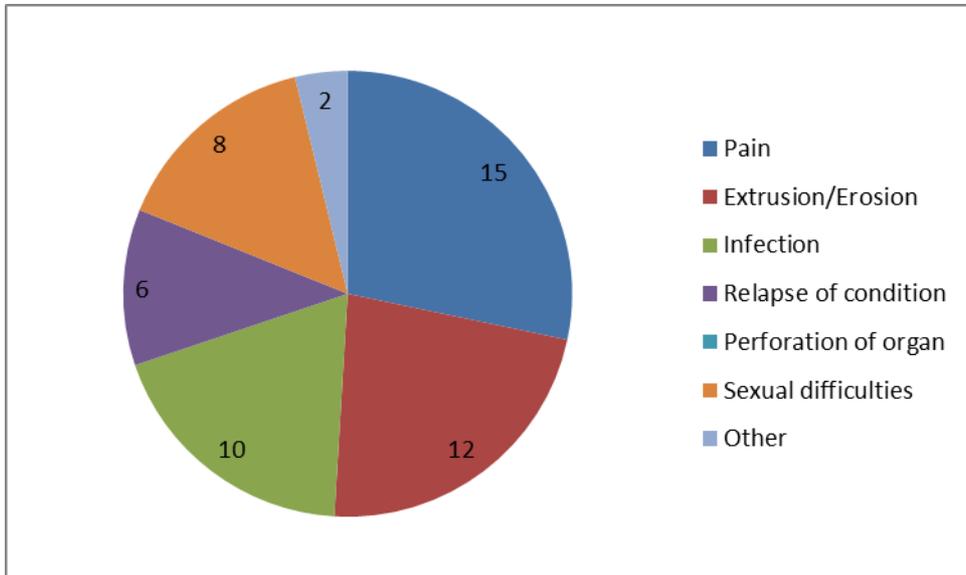
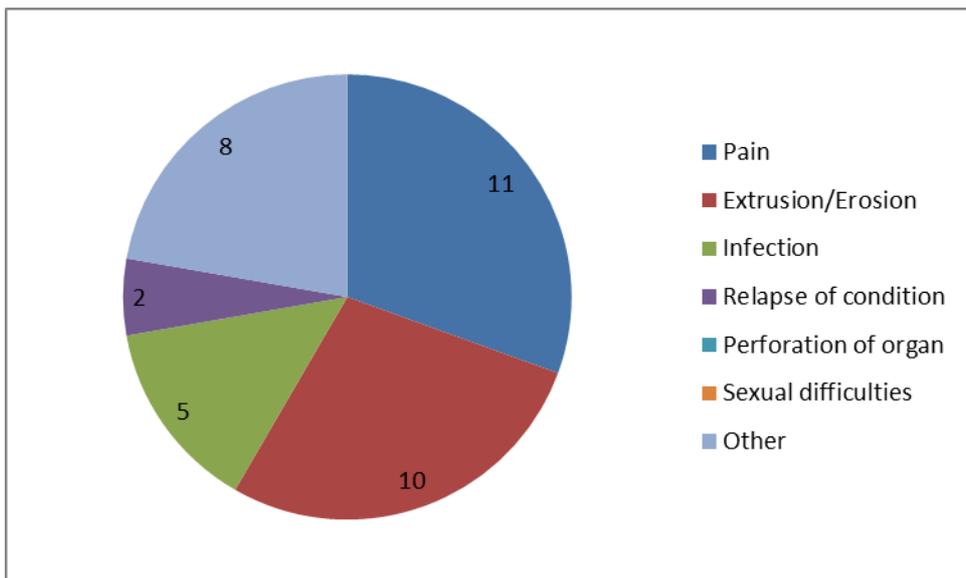


Figure 14 gives the number of incidents reported as vigilance reports. This does not include manufacturer vigilance reports for incidents we were already informed of from other voluntary sources.

Figure 14 Complications for POP implants reported by manufacturers



4.1.2 Adverse incidents reported to NRLS (formerly NPSA)

The National Reporting and Learning System (NRLS) was established in 2003 and manages a national reporting system on behalf of the NHS in England and Wales. The system enables patient safety incident reports to be submitted to a national database. These data are then analysed to identify hazards, risks and opportunities to improve the safety of patient care.

The NRLS was developed to promote comprehensive national learning about patient safety incidents. The NRLS receives reports about patient safety incidents from NHS organisations, staff and contractor professions, in confidence, on a voluntary basis. It is important to stress that, due to the voluntary nature of the NRLS; the data provided should not be considered representative of national trends in any way. Counts of incidents are simply incidents reported to the NRLS.

The NRLS is a dynamic data set – there is no limit on the age of incidents that are reported to the NRLS. This means that the NRLS could potentially receive incidents that are three or four years old. The data provided are, therefore, not static and is subject to change. The NRLS does not investigate individual incidents or individuals; this is largely the responsibility of local trusts and organisations. NRLS was aware that, due to an identified increase in numbers of adverse event reports concerning vaginal mesh implants, MHRA had initiated an investigation to better understand the use of these devices and the complications associated with their use. They, therefore, compiled a summary report of NRLS incident reports for MHRA in October 2012 (Figure 15).

Figure 15 Number of patient safety incidents relating to mesh used in gynaecological procedures reported to the NRLS

Number of patient safety incidents relating to mesh used in gynaecological procedures reported to the National Reporting and Learning System (year of occurrence by reported degree of harm)				
	No harm	Low	Moderate	Total
2006	2	0	0	2
2007	1	0	0	1
2008	1	0	1	2
2009	1	2	0	3
2010	1	2	6	9
2011	0	2	4	6
2012	7	4	3	14
2013	4	1	1	6
Total	17	11	15	43

Source NHS England

The conclusion given by NRLS was that many of the incidents identified contained descriptive data that were not relevant to the MHRA investigation or indicated broader clinical use issues that cannot always be directly linked to vaginal mesh implants.

4.1.3 Discussion of adverse incident data

Reported complications

From 2005 to 2013, MHRA received 291 adverse incident reports related to vaginal mesh implants for SUI and 110 reports on vaginal mesh implants for POP. Although these numbers are small in comparison to the numbers of devices understood to be implanted (see Section 4.2), it is clear the impact on the quality of life for some patients is severe.

The reports to us of adverse effects are written as subjective accounts and do not necessarily indicate the severity and how long the complications last for, and whether they are subsequently resolved or rectified. The terms we have used to group the common complications are based on our interpretation of these subjective accounts of the incidents. It is important to recognise that these reports cannot be regarded as a full assessment of the impact on the patient's quality of life.

The four incidents reported to MHRA where the patient died after surgery, were all in England, three related to vaginal mesh implants for SUI, and one to vaginal mesh implant for POP. From the information we have, all four deaths are consistent with complications related to the surgical procedure itself. This does not implicate the mesh implants in the deaths. All surgery has risks and underlying health conditions or other factors may also contribute to complications, including death.

Quality of data

The quality of reported information giving basic factual details about the mesh devices is variable and not always complete, which limits any kind of further investigation by manufacturers as part of their post-market surveillance activities.

Several reports from members of the public indicate that they do not know exactly what type of surgical procedure they have had and which vaginal mesh device they have had implanted such as the name of the device, manufacturer, model type, batch/lot number. It is clear that patients often do not have easy access to their medical records to obtain these details.

Some reports submitted by healthcare professionals conducting revision surgery, were not necessarily the original implanting surgeon and, therefore, they did not always have full access to device details such as the manufacturer or model.

We are aware that some clinicians are not clear as to what constitutes an adverse event with vaginal mesh implants and what type of adverse event they should report to MHRA. There are ongoing initiatives to improve this further for all medical devices (see section 8.2). It is also clear that Unique Device Identifiers (UDIs) are not always currently used with patients and, therefore, it is not always clear which patients have received which particular devices.

The scope of the investigations carried out by manufacturers is often very limited as often the vaginal mesh implant remains implanted and is, therefore, not available for analysis, or details the device cannot be clearly identified. Any investigation is also limited when patients do not give permission for some details to be passed to the manufacturer. Patient records are confidential and neither MHRA, nor the manufacturer can have access to them.

Increase in reports

MHRA fully recognises that adverse events are under reported for all medical devices, and we continue to pursue initiatives with NHS England and the Devolved Administrations to improved adverse event reporting from healthcare professionals. (See Section 8.2.1)

Figures 1 and 8 indicate an increase in the number of adverse incident reports received for both SUI and POP vaginal mesh implants since 2010, but this needs to be viewed with caution and cannot necessarily be interpreted as a rise in the occurrence of adverse event. This may be due to an increased awareness by patients, via patient support groups that have been set up, and increased media reporting of individual cases.

Although we fully recognise the limitations of interpreting data from these adverse incident reports to date, none of the final investigation reports has indicated that the devices have been inherently unsafe and required any enforcement action against the manufacturers by MHRA or removal from the market. However, many reports have been inconclusive, as there has not been enough information to be able to investigate the incident in-depth, although no fault has been attributed to the device.

4.2 Number of vaginal mesh implants in use – denominator data

4.2.1 Introduction

MHRA does not hold any information that indicates how many vaginal mesh devices have been implanted. However, information from other external databases and sources has helped to inform us how many vaginal mesh implants are likely to be in use.

4.2.2 Manufacturer sales figures

MHRA periodically requests sales figures from manufacturers known to supply the UK, in confidence, to give an indication of how many vaginal mesh implants may be in use. These figures give an understanding of the number of devices in circulation, but not necessarily how many have been implanted.

MHRA requested sales data from the leading manufacturers covering the time period 2005 to 2013. There may be other manufacturers who supply the UK market; however, we believe the numbers are small. The data in the tables below have not been broken down into individual manufacturers or models, due to the sensitivity of the information.

Vaginal mesh implants used to treat stress urinary incontinence (SUI)

Sales data were requested from seven manufacturers from 2005 to 2013. MHRA is aware that there are approximately 29 models on the market and approximately 170,433 units were sold in the UK and worldwide 3,668,400 units, during the specified time period.

Figure 16 UK Sales of SUI Implants

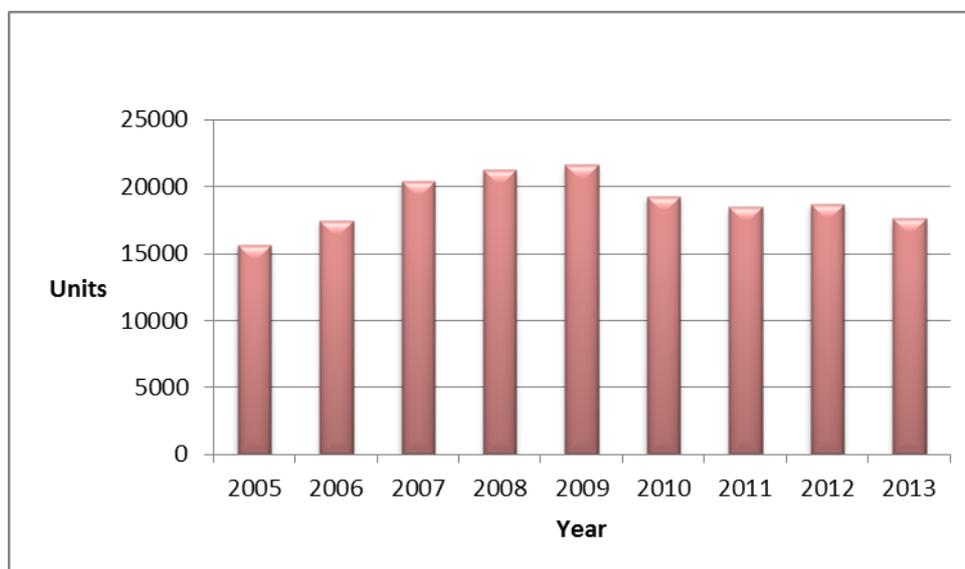
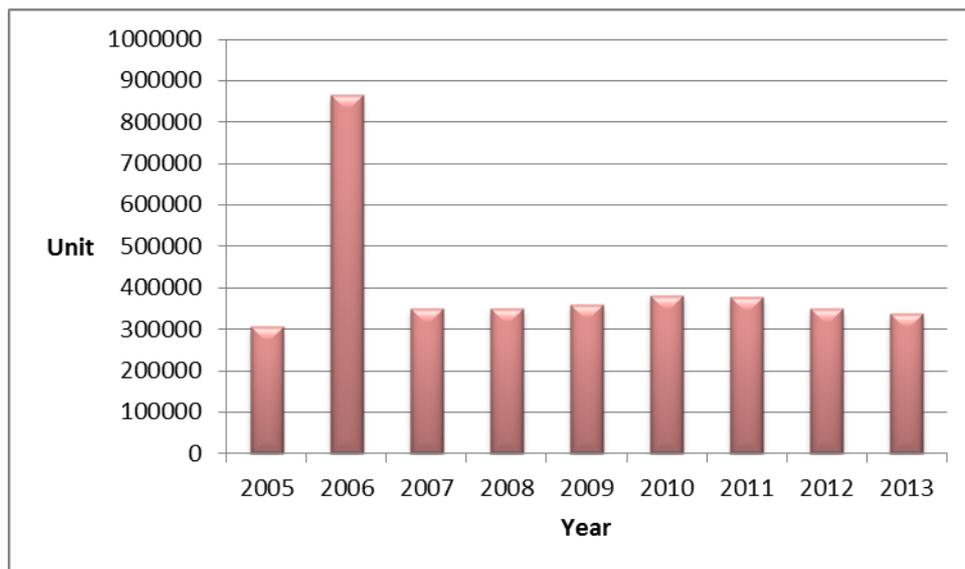


Figure 17 Global sales of SUI implants



Vaginal Mesh Implants Used to Pelvic Organ Prolapse (POP)

Sales data were requested from seven manufacturers from 2005 to 2013. MHRA is aware that there are approximately 25 models on the market and approximately 24,134 units were sold in the UK and worldwide 848,201 units during the specified time period.

Figure 18 UK sales of POP implants

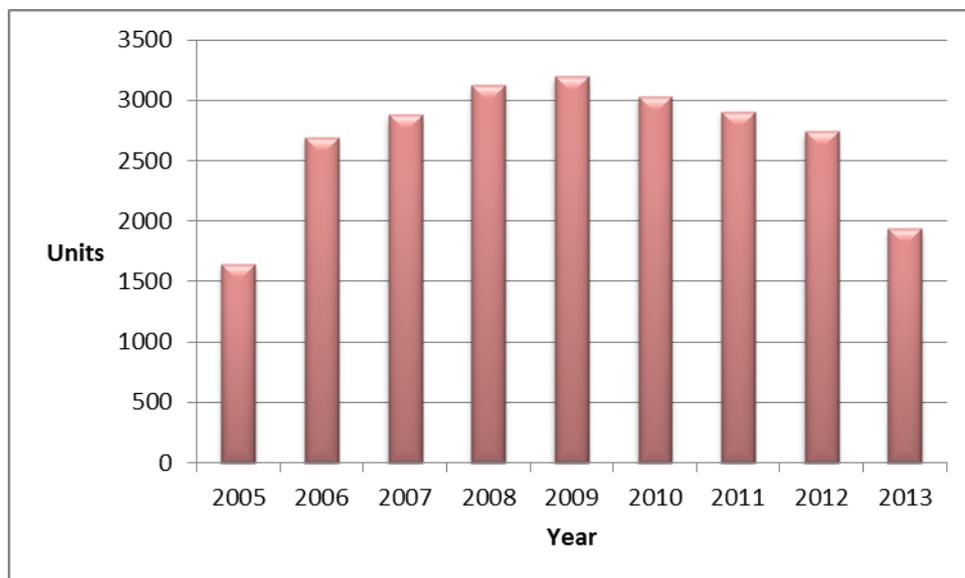
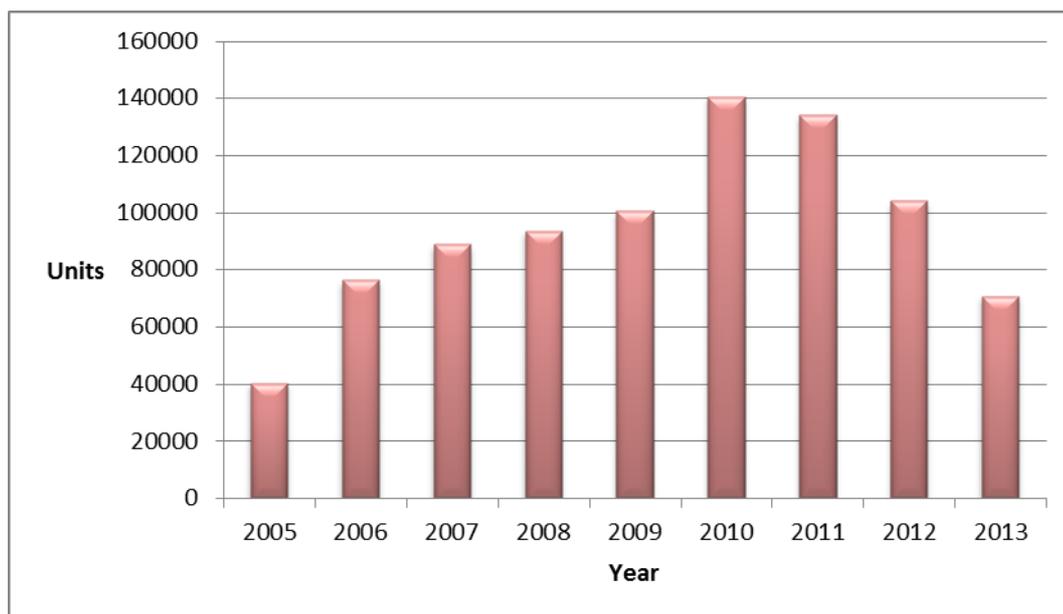


Figure 19 Global sales of POP implants



4.2.3 Health and Social Care Information Centre (HSCIC) and hospital episodes statistics (HES)

MHRA requested HES statistics from HSCIC on finished consultant episodes (FCE) for the insertion and removal of vaginal mesh implants to give an indication of how many of these operations were taking place. HES statistics are only available for England.

An FCE is a completed period of in-patient activity for a patient under one consultant within one healthcare provider. If a patient is transferred from one consultant to another, then the episode ends and another begins – even if this new spell is within the same provider unit.

Figure 20 lists the FCEs for the insertion of vaginal mesh implants for SUI in England from 2005 to 2013. Figure 21 indicates the FCEs for the removal of vaginal mesh implants, for SUI, in England from 2005 to 2013.

Our understanding is that the term ‘removal’ does not necessarily mean the whole mesh device has been removed. This coding is used by clinicians for procedures to trim very minor extrusions of a few mesh fibres and for procedures to remove larger amounts of mesh for pain.

Figure 20 Finished consultant episodes (FCEs) for women who have received a primary or secondary operative procedure for the insertion of transvaginal mesh, transobturator tape, transvaginal slings and transvaginal tape.

Procedure	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	Total
Insertion of transvaginal mesh	-	222	1,515	1,827	1,849	1,636	1,524	1,310	9883
Insertion of transobturator tape	-	2,580	5,045	5,750	5,569	5,426	4,885	4,476	33731
Insertion of transvaginal sling	279	277	210	151	141	130	134	135	1457
Insertion of transvaginal tape	-	6,137	8,817	8,503	8,397	8,087	8,172	7,627	55740
									100811

Note: Activity in English NHS hospitals and English NHS commissioned activity in the independent sector.

Figure 21 Finished consultant episodes (FCEs) for women with a primary or secondary operative procedure for the removal of transoburator tape and transvaginal tape.

Procedure	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	2012-13	Total
Removal of transoburator tape	-	68	79	96	128	95	96	124	686
Removal of transvaginal tape	-	287	417	506	475	508	565	581	3,339
									4,025

Note 1: Activity in English NHS hospitals and English NHS commissioned activity in the independent sector.

Note 2: There is no clinical coding available for the removal of transvaginal mesh or transvaginal slings.

Note 3: The figures do not represent the number of different patients, as a person may have more than one episode of care within the same stay in hospital or in different stays in the same year.

HES statistics for vaginal mesh implants for POP were also requested. Figure 22 lists the FCEs for the insertion of these devices in England from 2006 to 2012. Data related to removal of vaginal mesh implants for POP are not available.

Figure 22 Finished consultant episodes (FCEs) for women who have received surgical repair of vaginal wall prolapse using mesh.

Procedure	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12	Total
Anterior colporrhaphy with mesh reinforcement	142	704	908	873	729	695	4,051
Posterior colporrhaphy with mesh reinforcement	200	441	554	517	478	450	2,640
Repair of vault of vagina with mesh using abdominal approach	86	136	131	158	190	-	701
Repair of vault of vagina with mesh using vaginal approach	142	200	163	210	189	-	904
							8,296

By collating UK manufacturer sales data, MHRA incidents and HES data, it is possible to calculate a crude estimation of the denominator values for vaginal mesh implants for SUI and POP. However, it is important to bear in mind that HES data only covers England and the figures for POP cover 2006 to 2012.

Figure 23 Summary of UK vaginal mesh implant sales (2005 to 2013), adverse events reported to MHRA (2005 to 2013) and HES data for insertion and removals (England).

Vaginal mesh implant	Manufacturer sales (UK)	HES data Insertion (FCE) (England)	MHRA Incidents (UK)	HES data Removals (FCE) (England)
SUI	170,433	100,811	291	4,025
POP	24,134	8,296	110	-

4.3 Evidence from a UK notified body

The regulatory system for medical devices requires the involvement of independent, third-party, organisations called notified bodies, which perform pre-market assessment of medical devices. CAs, such as MHRA, designate and continuously monitor the continual performance of the notified body; ensuring they meet their designation criteria and that they carry out the relevant assessments to ensure that products being placed on the market are safe and effective. This is very different to pharmaceuticals where it is the CA who performs the pre-market assessment of products.

In accordance to the Medical Devices Directive (MDD) 93/42/EEC, the role of MHRA is to designate and monitor UK notified bodies for a particular scope.

A notified body must be qualified to perform all the functions set out in any annex for which it is designated. The designation may be restricted to specified types of devices and/or Annexes. All European notified bodies are in the process of or will be re-designated in accordance to the Commission Implementing Regulation 920/2013. The purpose of this is to ensure all notified bodies are working to the required standard.

Therefore, as the conformity assessment tasks are conducted by the notified body, MHRA would not be involved in the routine review of the manufacturers pre-market risk assessments carried out by notified bodies. However, during our continuous monitoring of the performance of notified bodies we do sample their client activity and would review client files in great detail to ensure compliance with the requirements.

All vaginal mesh implants on the EU Market are CE Marked in accordance to the MDD 93/42/EEC. These devices are classified as Class IIb medical devices in accordance to Rule 8 in Annex IX of the MDD 93/42/EEC. However, if any part of the device is absorbable they may be regarded as Class III medical device.

For Class IIb medical devices, the most common conformity assessment route involves an assessment of the manufacturer’s quality system in accordance to ISO 13485 along with the requirements in the relevant conformity annex of the directive, including design. In addition, they will sample across the range of products and processes to ensure that the requirements are being met. The manufacturer’s technical files will also be sampled in accordance to the Notified Bodies Operations Group (NBOG) best practice Guide 2009-4. The review of the technical file covers as a minimum:

- the intended use of the device including qualification as a medical device and its correct classification
- the validity of the essential requirements checklist, especially when harmonised standards have not been applied in full
- a review of the risk management file (which would comprise a thorough review of the clinical evaluation report and the risk–benefit analysis)

- pre-clinical data (studies in animal models, biocompatibility, and technical performance tests etc.)
- clinical evaluation in accordance with Annex X of the Medical Devices Directive 93/42/EEC (the notified bodies review would be in accordance to MED DEV 2.7.1 rev 3)
- information supplied by the manufacturer (label and Instructions For Use)
- declaration of conformity or the draft
- other technical documentation based on risk.

**** Section 4.3.1 is confidential under Article 20 of the Medical Devices Regulations****

4.3.1 Information MHRA requested from a UK notified body, [REDACTED]

MHRA requested information from the UK notified body [REDACTED] on their assessment of manufacturers they have certified in relation to vaginal mesh implants used to treat SUI and POP.

In particular we requested the following;

- any analysis of device technical files, in terms of risk assessment
- any review of the manufacturer's clinical evidence
- extracts from audit reports that contribute to the risk assessment of these devices
- any assessment of the manufacturer's post-market surveillance activities.

[REDACTED] provided us with information (see Annex G) of their assessments for three manufacturers:

- [REDACTED] – two POP vaginal mesh implants; one SUI vaginal mesh implant
- [REDACTED] – four POP vaginal mesh implants; three SUI vaginal mesh implants
- [REDACTED] – two POP vaginal mesh implants; one SUI vaginal mesh implant.

Manufacturer	POP mesh	SUI tape	Review of manufacturer's risk/benefit assessment	Date of any planned follow-up review
[REDACTED]	1		Accepted, with gaps identified which were raised as NCs. Corrective action plan provided.	2015
[REDACTED]	2		The risk assessment and conclusions drawn are considered satisfactory/acceptable	
[REDACTED]	1	3	Technical File to be reviewed in the future as a part of technical file sampling plan	
[REDACTED]	1	1	Minor NC raised – not meeting requirements of ISO 14971:2012	
[REDACTED]	1		Risk–benefit ratio remains favourable to the devices. Reviewed and accepted	
[REDACTED]		1	Major non-conformity raised in 2010 and subsequently closed. Due to lack of updates to risk management and clinical evaluation via PMS.	
[REDACTED]	2		Open non-conformity against risk management system	29 Sept 2014

NC = Non-conformity

4.4 Evidence from literature

4.4.1 Introduction

Evidence has been reviewed from published peer reviewed technical and clinical journals, articles and research.

4.4.2 Review of reviews reports from York Health Economics Consortium

4.4.2.1 Commissioning and protocol of the report

In February 2012, MHRA commissioned York University Health Economics Consortium to conduct a brief systematic review of reviews to explicitly identify, select, assess and summarise recent published systematic reviews related to the safety of vaginal mesh implants. The intention was to provide transparent, evidence-based information for the use of patient groups and policy makers.

The objectives of the review were to:

- identify systematic reviews published in the last ten years that evaluate the safety of these vaginal mesh implants
- summarise the data and conclusions from the systematic reviews, focusing on particular safety/adverse event outcomes of interest – including reviews that evaluate women who have had a vaginal mesh implant operation to treat urinary incontinence or pelvic organ prolapse
- present a brief overview of the results in light of the quality of the research.

4.4.2.2 The review of reviews report

The report was submitted to MHRA in April 2012 and presented data on the adverse effects and safety of vaginal mesh implants for female SUI inserted surgically via retropubic operations, fascial slings and mid-urethral synthetic slings, and for POP.

Extracts from the executive summary (see Annex C) are as follows:

Figure 24 Results – Percentage ranges of occurrences from individual Systematic Reviews (SR) showed the percentage of women who reported:

Complication	Percent occurrence for vaginal mesh implants for SUI	Percent occurrence for vaginal mesh implants for POP
Pain/discomfort after an operation	0% to 22%	1% to 25%
Sexual difficulties	3% to 10%	6% to 57%
Vaginal erosion	0% to 5%	-
Mesh/tape erosion	0.6% to 7%	0% to 10%
Bladder perforation	0% to 9%	-
Urinary tract infection	0.2% to 76%	-
Haematoma	0% to 4%	1% to 3%
Prolapse	0% to 16%	-
Recurrent prolapse	-	0% to 15.3%

The summary also reported that:

- **patient (subjective) reported cure rate** – 45% to 92% of women reported subjective cure (no incontinence). The short-term objective success rate ranged from 87% to 95% for mesh kits commonly used in the treatment of apical vaginal prolapse
- **quality of life data** – Quality of life data were assessed in 12 systematic reviews (SR). However, the data were not always reported, or could not be easily summarised
- **conclusions of the systematic reviews** – The SRs report on the effectiveness of one surgical treatment over another in terms of impact on SUI or prolapse and adverse effects. The SR

authors suggest that more long-term trials should be conducted to understand more fully the effectiveness and side effects if the different treatment options.

The discussion stated that in the last ten years, at least 17 systematic reviews have evaluated the safety of vaginal mesh implants.

SR findings may vary for a number of reasons including the specification of different inclusion and exclusion criteria such as whether included papers could be for women with SUI and mixed incontinence or for SUI alone.

This review has focused on Randomised Controlled Trial (RCT) data where possible, although it appears that the quality of these RCTs was variable based on the SR authors' assessments. In some of the SRs, data were gleaned from single trials, and pooling was not possible. Due to these limitations the findings were not pooled across SRs and the findings should be considered as indicative only and not used to statistically compare one procedure with another.

Overall, the quality of the SRs was good, providing confidence that the majority of relevant studies will have been included.

It is difficult to draw specific conclusions regarding the actual adverse event rates and subjective cure rates from the available literature for specific procedures. What the available evidence does suggest is the following:

- the majority of patients appear to find treatment beneficial in relieving their incontinence, although a significant minority do not report subjectively that treatment has cured their incontinence.
- rates of adverse events reported appear to be similar regardless of whether women are treated for SUI or POP. The exception would appear to be painful sexual intercourse which seems to be more prevalent with treatment for POP.
- evidence on adverse events suggests that whilst on the whole adverse events occur in only a minority of patients, the likelihood of such an event for an individual patient is not insignificant. However, the evidence is somewhat inconclusive as the ranges of rates of adverse events reported almost all include 0%. This suggests that some groups of patients may be more susceptible than others in developing adverse events or that surgical expertise and experience and patient after care – which may have differed across specific trials included in a review – may play a key role in developing adverse events.

4.4.2.3 Comments on the York 'review of reviews' report

The report was circulated for comment to MHRA external clinical contacts representing BAUS, BSUG and RCOG. Comments included the following:

- "We need to know the rate of complications of similar surgeries without mesh to compare these findings with".
- "There was a danger of double counting because reviews have access to only a limited pool of relevant RCTs, which must appear over and over in the reviews".

4.4.3 Summaries of safety/adverse effects report (the York report)

4.4.3.1 Commissioned further review work from York

MHRA then commissioned York to conduct another look at the reviews already identified to try to tease out some key messages for each of the outcomes of interest. These were presented as '[Summaries of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse](#)'.

They were developed using the data reported in SRs published in the last ten years and from studies which included more than 50 patients, because studies with fewer patients were not considered to be statistically robust.

The report was circulated for comment to MHRA external clinical contacts representing BAUS, BSUG and RCOG who assisted in drafting brief overviews of the report to go on MHRA's website and an overall summary table of the percentage complication rates found for various adverse effects from vaginal mesh implants.

MHRA was aware that there was a growing interest in the expected York Report and anticipated a lot of interest from the media and patient interest groups. Therefore, the publication date of the York Report was carefully planned with DH, the then NHS Commissioning Board and representatives from the clinical colleges and associations. Press notices were drafted and named clinical contacts from the Royal Colleges were placed on stand-by to be able to give radio interviews if necessary. Briefings were sent to Earl Howe and the NHS.

The report was published in November 2012 on MHRA's website along with a joint DH/MHRA press notice. On the same date a letter from Professor Sir Bruce Keogh (NHS England's Medical Director) and Professor Keith Willet (then the NHS National Clinical Director for Acute Episodes of Care) was sent to all NHS medical directors, urologists and gynaecologists drawing their attention to the York report, the associated NICE guidance for these procedures (see Section 5.3.3); and action agreed by DH, the then NHS Commissioning Board, MHRA and the relevant professional associations to reduce the rates of adverse events associated with vaginal mesh implants.

4.4.3.2 Summary of the literature review of vaginal mesh implants used for [SUI on MHRA's website](#)

Postoperative pain or discomfort after six months – In general the incidence of pain that persisted for more than six months after surgery was found to be low, affecting 1% or fewer of women, regardless of which type of operation was used. Groin or thigh pain, however, was mostly found after TOT surgery rather than the other types of incontinence surgery.

Erosion – This was the adverse effect that was reported in the largest number of studies but it was not common. As with the prolapse studies, there was a wide range of risk of erosion, probably resulting from differences in the ways this was diagnosed or recorded. The incidence (around 1 to 2%) was generally lower than after prolapse surgery.

Need for reoperation on vaginal mesh implants – Unlike the prolapse studies, this outcome is about data related to 'tape cutting, resection, ablation or repositioning' rather than about surgery for mesh erosion or removal of mesh due to erosion. For incontinence, it mostly relates to the tape being tightened too much and needing to be released; this might be regarded as a necessary but occasional result of over-supporting the urethra to prevent it leaking. On average one in 63 women might need some form of adjustment or further operation on the tapes.

Deterioration in sexual function at least six months postoperatively – Both painful sex and incontinence associated with sex was included in this analysis. The included studies suggested that these outcomes were not frequent.

Note: It is important to note that many women with incontinence or prolapse have considerable sexual problems prior to interventional surgery and for many of these the symptoms are improved following surgery, e.g., in the Ward Hilton trial, 70% reported that their sex life was spoiled by urinary symptoms preoperatively, compared to 27% at six months following surgery. In presenting findings for stress urinary incontinence (SUI), the data have been presented using the following groupings:

- Tension free trans-vaginal tape ('TVT') or supra pubic arch sling ('SPARC')

- Tape implanted through the obturator foramen using an inside out approach ('in-out TOT, including TVT-Obturator (TVT-O)' and tape implanted through the obturator foramen using an outside-in approach ('out-in TOT, including MONARC')

Figure 25 A summary table for reported complications for vaginal mesh implants to treat stress urinary incontinence from the York report is shown below:

		Post-operative pain/ discomfort after six months	Erosion	Deterioration in sexual function six months post-operatively	Need for reoperation on sling/tape	Organ perforation
TVT / SPARC	Percentage of women suffering complication	0.0%	1.1%	9.3%	0.9%	N/A
	Range	(0.0% to 1.5%)	(0.0% to 6.0%)	(3.8% to 13.5%)	(0.5% to 6.0%)	N/A
	Included studies	3	24	3	6	N/A
TOT	Percentage of women suffering complication	0.9%	2.4%	2.5%	0.0%	N/A
	Range	(0.6% to 5.1%)	(0.0% to 5.6%)	(1.9% to 3.2%)	(-)	N/A
	Included studies	4	25	2	1	N/A
Single incision system	Percentage of women suffering complication	1.1%	0.0%	No studies	No studies	N/A
	Range	(0.0% to 1.9%)	(-)			N/A
	Included studies	3	1			N/A
Sling (fascial / pubovaginal)	Percentage of women suffering complication	No studies	0.0%	No studies	No studies	N/A
	Range		(-)			N/A
	Included studies		1			N/A

4.4.3.3 Summary of the literature review of vaginal mesh implants used for [POP on MHRA's website](#)

Postoperative pain or discomfort after six months – while short-term pain or discomfort is to be expected after any type of surgery, pain persisting in the long term may affect a woman's quality of life. It was, therefore, disappointing to find that very little information was available in the literature review from seven studies: few women were affected but there was no comparable information about pain after prolapse surgery without mesh. This is not enough to inform practice, but suggests that persistent pain should be recorded in future research and registries concerned with the use of mesh/grafts or not in prolapse surgery.

Erosion – this refers to the exposure of mesh through the vaginal tissues sometime after surgery. While there was variation in the way this was recorded, this was the complication that was most often reported (in 51 studies). It may occur in around 1 in 15 women, but may be less common if a biological graft is used rather than a non-absorbable synthetic mesh.

Treatment for erosion – some (but not all) of the women who have mesh erosion need further surgery to remove some or all of the material. The evidence suggested that this might be around 1 in 20 or fewer. Clinicians have suggested that this may be a minor procedure in many cases. However, there have been some reports of severe morbidity, for example pain, that necessitated removal of large portions of mesh which may result in further problems or recurrence of the prolapse.

Organ damage – when women are having a mesh inserted during prolapse surgery, the mesh needs to be attached to other structures in the pelvis. Some nearby organs (such as bladder, bowel, nerves or blood vessels) may be damaged during this insertion. The evidence suggests this might happen in around 2% of cases. However, organ damage may also occur during non-mesh prolapse surgery.

Pain with intercourse after prolapse surgery – only three small studies reported rates of pain during intercourse after prolapse surgery. It was unclear whether they took account of pain women had before prolapse surgery, and there was no evidence about the number of women whose sexual function or pain had improved after surgery.

Note: It is important to note that many women with incontinence or prolapse have considerable sexual problems prior to interventional surgery and for many of these the symptoms are improved following surgery, e.g. in the Ward Hilton trial, 70% reported that their sex life was spoiled by urinary symptoms preoperatively, compared to 27% at six months following surgery

Figure 26 A summary table for reported complications for vaginal mesh implants to treat pelvic organ prolapse

		Post-operative pain/ discomfort after six months	Erosion	Deterioration in sexual function six months post-operatively	Need for reoperation on sling/tape /mesh	Organ perforation
Prolapse surgery: anterior/ posterior						
Synthetic non-absorbable	Percentage of women suffering complication	5.5%	6.5%	15.3%	4.8%	2.1%
	Range	(-)	(0.9% to 9.6%)	(12.8% to 17.7%)	(0.9% to 10.9%)	(0.9% to 2.8%)
	Included Studies	1	13	2	9	4
Biological absorbable	Percentage of women suffering complication	2.7%	1.2%	No studies	3.2%	0.0%
	Range	(0.8% to 7.5%)	(0.0% to 21.4%)		(1.0% to 5.4%)	(-)
	Included studies	3	7		2	1
Prolapse surgery: Uterine / vault						
Synthetic non-absorbable	Percentage of women suffering complication	2.0%	5.5%	14.5%	4.0%	1.8%
	Range	(1.2% to 2.3%)	(0.0% to 25.6%)	(-)	(0.8% to 7.1%)	(0.4% to 7.9%)
	Included studies	3	31	1	12	16
Biological absorbable	Percentage of women suffering complication	No studies	No studies	14.5%	No studies	No studies
	Range			(-)		
	Included studies			1		

4.4.4 Peer-reviewed scientific and clinical literature

MHRA maintains a general awareness of current research from peer reviewed professional journals and by attending professional based conferences. Where necessary, we query articles further with the author to clarify facts and evidence presented. Where some articles have suggested problems with the vaginal mesh implant or component, we have asked manufacturers to comment on this and how it may relate to their own products.

MHRA has an in-house library and information service giving full access to databases of scientific literature and electronic journals, where available. The principal biomedical databases available to staff are Embase, Embase Alerts and Medline accessed by using the ProQuest platform. These databases contain a range of bibliographic material, such as journal articles, conference papers, dissertations and reports. ProQuest offers a wide range of search options including citation searching, the creation of search alerts and literature searching.

MHRA subscribes to a number of relevant journals and also has access to the NHS Core Content journals. Articles not available on subscription are purchased for staff by the information services team. The team uses the resources of the British Library and has access to the resources of the BMA and RSM libraries. MHRA keeps up to date with the literature by creating alerts on ProQuest and also by using the 'Journal TOC' current awareness service.

MHRA has not commissioned any further systematic literature reviews, and are not aware of any significant peer reviewed articles published since the York Report was written.

We expect that the European SCENIHR review will take a further review of the most recent literature available and that this will complement the York Report. It is also clear that NICE guidance has taken account of recently published research papers.

4.5 Evidence from patients, members of the public and patient support groups

4.5.1 Introduction

MHRA has received information about patient experience with vaginal mesh implants in the form of adverse incident reports and correspondence with individuals from patient support groups. MHRA regularly reviews information available from patient support websites and discussion forums.

4.5.2 Adverse incident reports (also see Section 4.1)

Between 2005 and 2013, MHRA received 124 adverse incident reports from individual patients and members of the public involving vaginal mesh implants. Some of these reports are, however, from the same person reporting different medical conditions.

Some of the problems women have reported are severe and long-term, such as persistent pelvic and/or groin pain and dyspareunia. Many of the patient reported complications are not verified by clinical opinion that the vaginal mesh implant was the actual cause of the problem. These include examples of reported fibromyalgia or blurred vision. Despite the lack of verifiable evidence, MHRA treats these incidents seriously and all reports are kept on record should further scientific or clinical evidence emerge.

Every adverse incident reported to MHRA from a patient or member of the public is passed on to the manufacturer of the device concerned for the manufacturer to conduct further investigation and to contribute to their post-market surveillance, which is required under the MDD (see Section 2.1.9). Members of the public have the option to only allow the device details and the account of the adverse event to be given to the manufacturer. Personal details will only be sent if the member of the public has given consent for this.

If any of these adverse incident reports are subsequently determined to be vigilance reportable under the MDD, then the manufacturer has to inform MHRA and carry out an investigation as appropriate, and send a report with their conclusion and root cause analysis.

4.5.3 Individual correspondence from patients and members of the public

A number of individual women regularly correspond with MHRA about their concerns with vaginal mesh implants, often sending information such as copies of media reports, web links to medical articles and information from other countries worldwide. We review all the information brought to our attention, assessing it for whether it constitutes new robust evidence. If appropriate, we query the information further with mesh manufacturers directly. To date, all questions raised in this way have been resolved satisfactorily.

4.5.4 Patient support and campaign groups

A number of individuals have campaigned via their Members of Parliament (MP), who have then raised correspondence and parliamentary questions with DH and MHRA, asking about the safe use of vaginal mesh implants.

We are aware of the following groups and web based information sites that have been set up to support patients – mainly women – who have suffered from adverse consequences from vaginal mesh implant surgery.

4.5.4.1 UK based patient support groups

Meshies United

meshiesunitedgroup.co.uk

A few representatives of this group frequently correspond with MHRA, DH, NHS England and MPs and have recently gained significant access both to Government and senior personnel in the NHS. MHRA met with one representative in July 2012 who expressed her concerns about vaginal mesh implants

Two representatives of this group met with Earl Howe on 25 September 2013 along with Dr Catherine Calderwood NCD for Maternity and Women's Health, NHSE and John Wilkinson Director of Devices, MHRA. This was immediately followed by a separate meeting with Mr Wilkinson and the MHRA Head of Patient, Public and Stakeholder Engagement to address MHRA specific questions. They provided a list of questions at both meetings, which MHRA subsequently responded to.

TVT-Messed Up Mesh (MUM)

tvt-messed-up-mesh.org.uk

MHRA's then Medical Director, Dr Susanne Ludgate, met with two representatives in March 2012 in Bristol to listen to their concerns.

Scottish Mesh Survivors group's Hear Our Voice

This group is believed to be aligned with Meshies United. A few of their representatives presented evidence to the Scottish Public Petitions Committee on 3 and 17 June 2014.

TVT Info

tvtinfo.wordpress.com

This appears to be a web-based information and support page. We are not aware of any new evidence on this website.

Patient representatives from Meshies United, TVT-Messed Up Mesh and TVTInfo form part of the NHS England led working group – See section 8.3.1

4.5.4.2 International patient support groups

We are also aware of patient support groups and websites worldwide who exchange knowledge and information with UK based patient support groups. These include:

- The United States
TVT-NO!
[The Mesh Warrior](#)
- New Zealand
[Mesh Down Under](#)
- Canada
[I'm All Meshed Up](#)

4.6 Evidence from the clinical community

4.6.1 Introduction

MHRA has a Devices Clinical Director supported by a small clinical team. Vaginal mesh implants are used across a number of clinical disciplines: urology, urogynaecology and gynaecology. Therefore, the clinical team has open communication with the relevant professional clinical colleges and associations related to these disciplines, as well as fostering other clinical contacts.

4.6.2 Adverse incident reports

MHRA has received 118 adverse incident reports from healthcare professional/clinical users – see Section 4.1. They have been mainly from hospital clinicians with a few from GPs.

Every adverse incident reported to us from healthcare professionals is routinely passed onto the manufacturer of the device (if known) for their further investigation and to contribute to their post-market surveillance which is required under the MDD (see Section 2.1.9). If any of these reports are subsequently determined to be vigilance and reportable, under the MDD, then the manufacturer has to inform MHRA and carry out an investigation as appropriate, and send a report with their conclusion and root cause analysis where this is possible.

4.6.3 Information and statements from professional clinical colleges, societies and associations

Conferences attended by MHRA

MHRA attended BAUS and RCOG conferences in 2013 – there was much discussion about the use of vaginal mesh implants, and knowledge of patient concerns. However, there were no indications of vaginal mesh implants being unsafe.

There were views expressed that there was a need for evidence of performance from longer term clinical trials.

Royal College of Obstetricians & Gynaecologists (RCOG) and the British Society of Urogynaecology (BSUG)

When the York Report was published by MHRA in 2012 (see Section 4.4.3), RCOG issued the following [position statement](#) in support of the report:

‘Women seeking treatment for incontinence and prolapse should discuss all the options with their doctors including conservative non-surgical interventions. Surgical procedures can improve symptoms for certain women. However, women need also to know that any operation carries some risk whether with or without the mesh described in this report.

‘The RCOG welcomes this report. It is important that clinicians adhere to the NICE guidelines and inform patients of the risks and benefits of any procedure.’

A letter from **RCOG** and co-signed by **BSUG**, **EUGA** (Professor Linda Cardozo) and **IUGA** sent to all their members (Annex D) in June 2014 referring to the Scottish Government request to Health Boards to suspend vaginal mesh implants stated:

“The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing has changed since a letter was sent out to all practitioners before Christmas from Bruce Keogh, co-signed by myself”.

Dr David Richmond, President, Royal College of Obstetricians and Gynaecologists

British Association of Urological Surgeons (BAUS)

BAUS wrote to all their members (see Annex E) in June 2014 referring to the Scottish Government request to Health Boards to suspend vaginal mesh implants stated:

“The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing had changed since a letter was sent out to all practitioners in December 2013 from Sir Bruce Keogh”.

International Urogynecological Association (IUGA)

In July, 2014, IUGA released a [position statement](#) on mid-urethral slings (MUS) for stress urinary incontinence, which included the following statements:

“There is robust evidence to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use.”

“IUGA supports the use of monofilament polypropylene mid-urethral slings for the surgical treatment of female stress urinary incontinence”.

The Scottish Pelvic Floor Network (SPFN)

This is a group of clinicians and surgeons who wrote to their members (see Annex F) stating:

“In line with the National Institute of Clinical Excellence Guideline CG171, the Management of Urinary Incontinence in Women, the SPFN supports the use of Synthetic Mid-Urethral Slings in surgical treatment of stress urinary incontinence in women wishing to proceed for surgical treatment after failure of the conservative treatment options. The SPFN also supports the current credible medical research in this field”.

4.7 Evidence from industry

4.7.1 Introduction

Manufacturers of vaginal mesh implants keep data related to the safety and performance of these devices. This information has either been provided to MHRA by the manufacturers through regulatory obligations to report to us, and/or from direct requests to a manufacturer for information. Some information has been provided by one of the UK notified bodies known to have certified vaginal mesh implant manufacturers.

4.7.2 Manufacturers of vaginal mesh implants

The main manufacturers who currently supply a number of different types of vaginal mesh implants in the UK are:

- American Medical Systems (AMS)
- Bard Europe
- Boston Scientific
- CL Medical
- Covidien
- DIMA SL
- Ethicon – a Johnson & Johnson company

4.7.3 Compliance with the Medical Devices Regulations (MDR)

As far as MHRA is aware, all vaginal mesh implants available on the market in the UK are CE marked, therefore indicating that they are acceptably safe and fit for their intended purpose, and fully comply with all the relevant requirements of the MDR – see Section 2.

The manufacturers will have declared conformity with the regulations and demonstrated that their devices meet the essential requirements, such as biocompatibility, toxicity, technical specifications, clinical data, sterilisation, right through to packaging and labelling. They must also have assessed that the benefits to patients of their using the devices outweigh the identified risks.

All of the vaginal mesh implants are CE marked, and the majority are Class IIb medical devices which means a notified body will have sampled across the range of a manufacturers products and processes to ensure that the essential requirements of the Medical Device Directive are being met. The manufacturer's technical files will also be sampled which will include a review of the risk management file.

4.7.4 Vigilance reports (see Section 4.1)

Manufacturers' vigilance reports of adverse incidents are recorded on MHRA's AITS database – see Section 4.1 Adverse incident reports for the data.

Every adverse incident reported to MHRA from healthcare professionals and members of the public is routinely passed onto the manufacturers for their further investigation and to contribute to their post-market surveillance which is required under the MDR (see Section 2.1.9).

If any of these reports are subsequently determined to be vigilance reportable under the MDR then the manufacturer has to inform MHRA and carry out an investigation as appropriate, and send us a report with their conclusion and root cause analysis.

To date, none of the final investigation reports has indicated that the devices have been inherently unsafe and required any enforcement action against the manufacturers by MHRA or removal from the market. However, many reports have been inconclusive, as there has not been enough information to be able to investigate the incident in-depth, although no fault has been attributed to the device.

**** Section 4.7.5 is confidential under Article 20 of the Medical Devices Regulations****

Confidential under article 20 of the Medical Devices Regulations

4.7.5 Examples of safety information requested from manufacturers

Due to our awareness of increasing concerns with vaginal mesh implants, we have contacted known manufacturers on a number of occasions requesting technical or safety related information.

4.7.5.1 Specific request to some manufacturers asking about the safety of the polypropylene component of their mesh,

Below are extracts from two manufacturer's responses to this given in confidence to MHRA:

Manufacturer – [REDACTED] – The contention that polypropylene used in [REDACTED] meshes – one of the most common and widely used surgical implant materials – should not be used in the human body is completely refuted by the weight of scientific and clinical evidence, which for decades has demonstrated that polypropylene implants are safe and effective for medical applications in humans. Hundreds of clinical studies in reputable journals and medical texts affirm the safety of polypropylene mesh for medical use in humans, including those marketed by [REDACTED]

Prior to selling its polypropylene mesh devices, [REDACTED] complied with rigorous regulations and standards adopted by many regulatory agencies around the world, including those in European Union and the US, for assessing the biological safety of mesh products for human use. [REDACTED] has CE marked its mesh implants in accordance with the requirements of the European Medical Device Directive, 93/42/EEC after evaluation of scientific data, including substantial biocompatibility testing. This biocompatibility testing has been undertaken in accordance with standard EN ISO 10993-1 for Biological Evaluation of Medical Devices

[REDACTED] firmly believes that the use of polypropylene in humans, in the form of mesh implants, is not only appropriate, but also is one of the most beneficial materials that aid physicians in their care and treatment of patients.

Manufacturer – [REDACTED] – ‘The composition of the mesh used in [REDACTED] ... is the same biocompatible material as [REDACTED] both of which have been extensively tested as part of the [REDACTED] New Drug Application filed with the FDA and approved in 1969.’

.....
‘Further the FDA determined that any degradation of generic polypropylene sutures (not [REDACTED] which contains antioxidant) is clinically insignificant. Medical and scientific studies have never attributed any clinical significance to any degradation of [REDACTED] Indeed, non-absorbable sutures, such as [REDACTED] have been safely used in the human body for close to 45 years.’

‘As you are likely aware, every urological or urogynecological organization addressing this issue strongly supports the safety and efficacy of polypropylene mid-urethral slings as an appropriate option for physicians in the treatment of their patients.’

‘Particle loss can occur if a [REDACTED] is improperly manipulated or stretched beyond the elastic properties that are present when used in a clinical setting. This type of manipulation is not representative of how the product is handled by surgeons implanting it during a surgical procedure.’

4.7.5.2 General requests to all manufacturers of vaginal mesh implants

May 2010

MHRA wrote to known manufacturers, [REDACTED] and [REDACTED] [REDACTED] requesting information related to their vaginal mesh implants to treat incontinence. We asked for:

- their explanation for fewer reports of complications compared to the FDA
- sales figures for the last five years
- the number of incident reports they have received over the last five years, and their rationale for not reporting as vigilance to MHRA, if they had not done so
- a copy of the clinical data that were submitted to their notified body to support the CE mark of the device
- details of their post-market surveillance (PMS) plan for vaginal mesh implants

January 2012

Comments were requested from a few manufacturers on a 2009 paper in the International Journal of Urogynaecology indicating that Polyethylene terephthalate (PET) mesh implants degraded less than Polypropylene; and for details on any testing they have carried out to investigate whether the SUI vaginal mesh implants can shrink.

Responses indicated that there was no evidence that the mesh material shrinks, but a suggestion that tissue response, collagen deposition, causes tissue to retract.

February 2012

MHRA wrote to four manufacturers known to supply the UK with vaginal mesh implants – [REDACTED] and [REDACTED] asking for

their technical documentation to support complying with the Medical Device Regulations for three named devices randomly selected. We requested the following:

- clinical evidence – the clinical data and clinical evaluation report
- details of their post-market surveillance system and their management review of data collected to date
- their UK/EU/Worldwide sales figures for the last 10 years for vaginal mesh implants

The information provided by the individual manufacturers was analysed and no obvious concerns were noted. The majority of the clinical evidence was literature based. Evidence was provided of their PMS systems.

December 2013

MHRA requested, from seven known manufacturers, the following information:

- outcomes of any Post-Market Clinical Follow-up undertaken
- summary of their post-market surveillance (PMS) activities
- the most recent analysis of their PMS activity
- their most up to date risk assessment for vaginal mesh implants
- in relation to the above requests, how they had taken account of:
 - i. Hospital Episode Statistics (HES) data on the number of operations associated with the removal or partial removal of these implants in England, and
 - ii. information from the 'York Report' published on MHRA's website in November 2012

MHRA's detailed assessment of the requested information:

As part of the MHRA's review of vaginal mesh implants used in urological and urogynaecological surgery, information regarding post-market surveillance procedures held by the seven main manufacturers was reviewed. It contained comprehensive literature reviews, post-market surveillance data, vigilance, clinical trial data and risk conclusions. The information was found to be consistent with that which has been separately reported by a sampled notified body (NB) (see Section 4.3.1) and met with the relevant requirements for class IIb devices under current legislation. This sample covered the largest European NB and the three manufacturers with the worldwide largest market share of tapes and meshes sales used in this type of surgery.

4.8 Evidence from Europe

4.8.1 Introduction

MHRA works in close collaboration with other member states of the European Union (EU) by exchanging data related to the safety and performance of all medical devices.

This can take the form of direct requests for information between other EU countries, participating in European Commission Working Groups and by monitoring official government websites.

4.8.2 Information provided

4.8.2.1 MHRA general request to all EU competent authorities (CA)

MHRA sent a formal request to all other European CAs in September 2011 asking for information on vaginal mesh implants for SUI and POP. This included:

- how many incidents had reported to them?

- what failures reported most frequently?
- how many implanted annually?
- which manufacturers sell in their countries?
- any trends regarding failures?
- had any advice been issued in their countries?
- do they have any registers for these devices?

Denmark, Estonia, France, Ireland, Norway, the Netherlands, Poland, Switzerland and Sweden responded to the MHRA request and the information is summarised in Annex H.

No CA had issued any advice to its health service, although Ireland had distributed a copy of the US's 2008 FDA Public Health Notification and their subsequent updated 2011 notice (see Section 4.9.2.2.). The Netherlands were considering doing so and France referred to a report published in 2005 (see below).

No CA had figures for the number of vaginal mesh implants implanted, although the Netherlands provided sales figures that they were aware of.

The incident type failures reported were: erosion into the vagina, infection, rejection, severe pain, migration, abscess, dyspareunia, bleeding, urinary retention, fever, ileum perforation, sepsis, ureteral injury, incontinence not resolved, re-operation/removal of (parts of) mesh, and decrease in quality of life.

Switzerland reported two deaths during surgery for SUI; however, it is not clear whether this is because of the surgery itself.

Most CAs had very few reported incidents. France had the highest figures with totals of 69 for POP from 2004 and 212 for SUI from 2001.

No CA had National Registries; however, the Netherlands said that recently the Dutch Society for Gynaecology and Obstetrics (Nederlandse Vereniging voor Obstetrie en Gynaecology – NVOG) has initiated the Foundation Registry Complications of Gynaecologic Interventions (Stichting Complicatieregistratie Gynaecologische Ingrepen Nederland). This registry is broader than this device alone.

4.8.2.2 Published Reports by EU countries

The Netherlands

A report '[Transvaginal Mesh: Serious Complications Demand Cautious Use](#)' produced and published by the Dutch Health Care Inspectorate in July 2013 stated the following:

'Health care providers are becoming increasingly aware of the risks related to mesh. It must however also be mentioned that many women benefit from the intervention. A ban on either mesh or the intervention would thus lead to negative health results. Nevertheless, caution is warranted and improvements to the application of mesh are necessary. Among others, laws regulating medical devices need to be tightened, clinical research relating to the effectiveness of medical devices before their market introduction must be improved, and health care professionals must be obliged to report incidents related to medical devices.'

France

A report published by AFFSAPS (in French) in 2005 did not provide any new information.

Denmark

In [August 2012](#), the Danish Health and Medicines Authority, advised hospitals in Denmark to call in women, who had vaginal mesh implants for POP, for consultation in response to concerns raised by the

authorities in other countries. The concern did not affect women who had vaginal mesh implants for SUI.

4.8.2.3 European Commission competent authority (CA) vigilance meetings

Vaginal mesh implants were first discussed in April 2012 at a European Commission (EC) Medical Devices Vigilance Group meeting, and has been a standing agenda item at these monthly teleconference meetings since mid-2013 so that member states have an opportunity to share any new information.

In April 2013 an EC coordinated Meshes Task Force was formed involving the UK (MHRA), Denmark, Sweden and the Netherlands to explore the issues and uncertainties with vaginal mesh implants. This included expert input from European surgical associations to explore the issues and uncertainties related to these devices.

A mandate of work was put to the European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in March 2014 asking for a scientific opinion on '[The safety of surgical meshes used in urogynecological surgery](#)'. This is due to report back in January 2015

MHRA passed on to SCENIHR the Protocol and the two reports produced by York; the initial 'Review of Reviews' which includes the comprehensive list of referenced systematic review articles and, the final published 'Summaries of Safety/Effects'.

4.9 Evidence from the United States and worldwide

4.9.1 Introduction

MHRA is committed to collaborating with other CAs on a global scale and has developed formal contacts with worldwide counterparts as well as observing official government websites.

4.9.2 United States: Food and Drug Administration (FDA)

4.9.2.1 Adverse incident reports in the US

The FDA operates a Manufacturer and User facility Device Experience (MAUDE) database. This database houses medical device reports submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers.

4.9.2.2 FDA health notices and official statements

In Nov 2012 MHRA's liaison contact within the FDA provided us with the following summary of official notifications issued by the FDA and action being taken:

'On July 13, 2011, based on an updated analysis of adverse events reported to the MAUDE database and complications described in the scientific literature, the FDA issued a Safety Communication titled '[UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse](#)' to inform the medical community and patients that:

- serious complications associated with surgical mesh for vaginal repair of POP are not rare (contrary to what was stated in the 2008 PHN), and
- it is not clear that transvaginal POP repair with mesh is more effective than traditional non-mesh repair.

On [September 8-9, 2011, the FDA convened its Obstetrics & Gynecology Devices Panel](#) [**Note : MHRA also attended this meeting**] to obtain input on the safety and effectiveness of vaginal mesh implants used for urogynecologic indications and its proposed pre-market and post-market regulatory strategies for these devices. The panel consensus was that the safety and effectiveness of surgical mesh indicated for vaginal repair of POP and a subset of surgical mesh indicated for SUI (i.e., mini-slings) have not been established. The panel recommended that pre-market evaluation of surgical mesh

indicated for vaginal POP repair and mini-slings should include an analysis of data from prospective, controlled, clinical studies. The panel also recommended that the FDA issue post-market surveillance study orders ('522 orders') for these devices. The panel further recommended that the FDA reclassify surgical mesh indicated for vaginal repair of POP from Class to Class III. Regarding surgical mesh indicated for sacrocolpopexy (i.e., abdominal repair of POP) and multi-incision slings indicated for SUI repair (i.e. retropubic and transobturator slings), the panel consensus was that the safety and effectiveness of these devices are well established.

Based on the panel's input, on January 3, 2012, the FDA issued eighty-eight (88) 522 orders for surgical mesh indicated for vaginal repair of POP and eleven (11) 522 orders for single incision mini-slings. The FDA is currently working with individual manufacturers to develop study designs that will address the public health questions raised in these orders. In addition, the FDA is currently evaluating the panel's recommendation to reclassify surgical mesh indicated for vaginal POP repair from Class II to Class III.'

As a result of the 522 orders and the panel's recommendation to reclassify, a number of manufacturers elected to (1) stop marketing surgical mesh indicated for transvaginal POP repair or (2) no longer indicate their surgical mesh products for transvaginal POP repair. The manufacturers made those business decisions independently and then subsequently notified the FDA. However, the FDA has no plans to withdraw urogynecologic surgical mesh for any indication from the market because, based on our assessment of the published literature, input from clinical organizations, and the panel's recommendations, we believe there are patients who can benefit from surgical mesh used for transvaginal repair of POP.'

4.9.2.3 Recent 2014 announcement

On [29 April 2014](#) the FDA issued proposals to reclassify surgical mesh for transvaginal POP from a moderate-risk device (class II) to a high-risk device (class III) and require manufacturers to submit a pre-market approval (PMA) application for the agency to evaluate safety and effectiveness.

4.9.3 Australia – Therapeutic Drugs Administration (TGA)

In [October 2012](#), TGA published information on their website giving background information on urogynaecological surgical mesh implants. A detailed clinical review was undertaken in 2010 and found that compared to the number of women who had received a vaginal mesh implant insertion, the number of complications was low. In addition, the complication rate did not appear to differ between products, but factors such as the skill and training of the surgeon, selection of the patient and procedure were important. This outcome was endorsed by the Medical Device Incident Review Committee, an independent group of experts that advised TGA on medical device post-market issues.

The TGA review took into account the 2010 Cochrane Review of the surgical management of pelvic organ prolapse in women which examined some forty randomised controlled trials, evaluating 3773 women. TGA also worked with the relevant specialist societies.

TGA published further information on their website in [May 2014](#), informing that they had subsequently undertaken a further review of urogynaecological surgical mesh implants and established the Urogynaecological Devices Working Group (UDWG) to advise on this work. The working group met in August and October 2013 and there will be further meetings in 2014 during the course of the review.

This ongoing TGA review will advise on whether the adverse events associated with urogynaecological devices have occurred due to the design and/or the materials used; or whether other factors, such as devices being supplied and/or used inappropriately, patient characteristics or training experience, are contributing to these adverse events.

On 20 [August 2014](#), TGA announced that they will be reviewing clinical evidence for the use of vaginal mesh implants in some women. TGA have not suspended the use of vaginal mesh implants which can continue to be used in Australian women. The TGA report highlights the importance of patient selection, surgeon experience and informed consent.

MHRA has asked for a copy of the report so that we can assess any impact on these devices in the UK.

4.9.4 New Zealand – Medsafe

On 2 July 2014 a patient group presented a submission to [Parliament's health select committee](#) in Wellington, urging the Government to take action. The committee decided that the petition needed further consideration and will be reviewed in the new Parliament.

From a revised statement on their website [May 2014](#), Medsafe stated:

'Medsafe continues to monitor adverse event reports relating to the use of surgical mesh implants for the treatment of pelvic organ prolapse, stress incontinence and/or hernia repair. Concerns have been raised by some regulators about such mesh implanted transvaginally to treat certain conditions. Medsafe has concluded that surgical mesh is safe when used in accordance with the manufacturers' instructions by an appropriately trained surgeon. This conclusion is in line with that of other device regulators and professional bodies. Medsafe notes that surgical mesh remains approved for use by medical device regulators globally.'

Medsafe investigations

In 2008, a review of reports of adverse events relating to urogynaecological surgical mesh implants was conducted by Medsafe. This investigation included a literature review of papers published on this subject.

The report was submitted to the Medical Device Incident Review Committee, an Australian advisory committee with representatives from several Professional Colleges, for review along with a report on the same subject from the Therapeutic Goods Administration Medical Device Incident Review and Investigation System. The committee concluded that the return of symptoms and erosion (into the vagina or rectum) were the most common problems associated with these devices and that there was a need to explain this to the patient in terms of the success rate they could expect. It also noted that training of surgeons was important to the success of this new type of surgery.

4.9.5 Canada – Health Canada

In [February 4 2010](#), Health Canada issued a notice to hospitals giving important safety information on vaginal mesh implants for SUI and POP. In the notice it stated that Health Canada was concerned about Canadian and international reports of various intraoperative and postoperative complications associated with the use of these medical devices. In light of this, they recommended the following:

- review the labelling of relevant devices, especially sections concerning warnings, precautions and adverse reactions
- inform patients during the pre-surgical consultation of adverse events that may occur. Though transvaginal implantation of surgical mesh is generally considered permanent, patients should be aware of the possible need for additional surgical procedures that may not always fully correct some potential complications
- be observant both intraoperatively and postoperatively for signs of any complications associated with transvaginal mesh placement
- be aware of and/or get training on proper case selection, initial implantation procedure and management of complications.

A further notice was issued to hospitals, on [May 13 2014](#) stating:

'...that although many women treated with these devices have had good outcomes, Health Canada continues to receive reports of complications, including some serious and life-altering events, associated with the use of these surgical devices.'

Hospitals were given recommendations for surgical procedures involving vaginal mesh implants, to conduct pre-operative counselling to inform patients about all treatment options and to ensure that patients were fully aware of the potential risks and benefits of each treatment option and provide patients with written documentation including device labelling when available.

In a separate notice on [May 13 2014](#), Health Canada stated:

'Health Canada is reviewing labelling related to these products to determine if it provides appropriate safety information. Additional safety information in the labelling will be requested, as needed.

It is important to recognize that there is a risk of complications with any surgical procedure. Some of these complications can also occur with non-mesh surgery. There may be some similar risks when using transvaginal mesh devices to treat POP and SUI, but the complications differ in their severity, how frequently they occur, and how they are managed.'

The notice ended with Health Canada stating that they continue to monitor the safety of surgical mesh devices for the treatment of SUI and POP.

4.10 Evidence from registries

There is currently no national registry in the UK where clinicians have to input data relating to surgical procedures involving vaginal mesh implants.

MHRA's view on setting up a registry is that the decision will need to be led by the clinical community because any registry must provide outputs that can be used to improve patient care. MHRA would want to influence the establishment and design of any registry for procedures involving medical devices in order to ensure that the data collected are appropriate for post-market analysis related to the safety of the devices involved. For example, the National Joint Registry is a successful registry that provides valuable information for clinicians and the MHRA about the long-term performance of knee and hip implant procedures.

There is an existing BSUG database, currently being used by 20-30% of urogynaecologists, which could be adapted to record procedures, complications and some outcome data for specific urogynaecological procedures, including vaginal mesh implant insertion procedures.

Discussion on a national registry is ongoing and is facilitated by NHS England. Those involved in the discussion are the specialist societies i.e. BSUG, BAUS, RCOG and MHRA.

5 Additional information related to vaginal mesh implants

Key points

- MHRA hosted two workshops in 2011 and 2012 to better understand the issues related to the safe use of vaginal mesh implants. Clinical and manufacturer representatives attended
- NHS Choices website, NICE guidance and specialist professional clinical websites provide comprehensive information for patients on vaginal mesh implants
- manufacturer instructions for use (IFU), NICE guidance, Department of Health, NHS England and specialist professional clinical websites, provide information for clinicians related to vaginal mesh implants
- MHRA is aware of two potential patient class actions being prepared in the UK. There are several ongoing individual legal actions in the US.
- there has been considerable tabloid media coverage in Scotland, but very little for the rest of the UK
- MHRA has been working very closely with Scottish government on the issues raised with women in Scotland
- there are a number of ongoing projects and research on vaginal mesh implants that are expected to provide useful data.

5.1 MHRA workshops

5.1.1 Introduction

When MHRA first became aware of issues related to vaginal mesh implants from women who had experienced severe adverse events, we had received very few reports of adverse incidents. To better understand the issues related to the safe use of vaginal mesh implants, MHRA hosted two workshops. The first workshop was held in March 2011 and examined issues related to vaginal mesh implants for SUI. The second was held in March 2012 and looked at vaginal mesh implants for POP. The workshops included invited clinical representatives from RCOG & BSUG, BAUS, and some manufacturer representatives.

5.1.2 [Workshop on issues involving vaginal mesh implants used to treat stress urinary incontinence.](#)

The meeting covered:

- product development
- introducing a new device into clinical practice
- device implantation in a safe environment
- reporting of patient outcomes and adverse events
- responsibilities of involved parties (clinicians, regulators and manufacturers).

An article summarising the discussions was published in the journal European Urology which summed up expected responsibilities of the parties involved in the manufacture, regulation and surgical provision of vaginal tapes:

Abrams P, et al. Synthetic Vaginal Tapes for Stress Incontinence: Proposals for Improved Regulation of New Devices in Europe. Eur Urol (2011) [European Urology website](#).

Another outcome was that BAUS, in conjunction with MHRA, published a patient information leaflet intended to supplement any advice patients may already have been given by their GP or other healthcare professionals.

5.1.3 Workshop related to issues involving vaginal mesh implants used to treat pelvic organ prolapse.

Representatives were also present from NICE, (██████ notified body) and a representative from the ongoing PROspect research project (see Section 8.4.1).

An outcome from the workshop was that a number of recommendations to the parties involved in the manufacture, regulation and surgical provision were drafted and placed on the MHRA website.

5.2 Guidance available to patients on vaginal mesh implants

5.2.1 Introduction

Patients with concerns or queries about their health and treatment involving vaginal mesh implant should always contact their GP or surgeon in the first instance. In addition, there are also other official sources of advice and guidance available to them about vaginal mesh implant surgery.

MHRA has received many queries from women with concerns about vaginal mesh implants, and we have website pages aimed at patients with information including a summary of the York Report (see Section 4.4.3.): '[Vaginal tapes for stress urinary incontinence: Information for patients](#)' and '[Vaginal mesh for pelvic organ prolapse: Information for patients](#)'.

Our patient focussed website pages are expected to be removed by 2015 and transferred to the NHS Choices website. There are several other official clinical sources of information available to patients and members of the public on vaginal mesh implants.

5.2.2 NHS Choices website

[Urinary incontinence – surgical treatment](#) – Includes information on tape procedures for women
[Pelvic organ prolapse – treatment](#) – Includes information on surgical repair and vaginal mesh.

5.2.3 NICE guidelines

NICE 'interventional procedures guidance' advises the NHS on when and how new procedures can be used in clinical practice. It makes recommendations on the safety of a procedure and how well it works. Some guidance is written because the procedure is quite new which means there is not a lot of information yet about how well it works, how safe it is and which women will benefit most from it.

The independent experts who write the NICE guidance (advice) for the NHS include healthcare professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is, and ask the opinions of expert advisers.

There are leaflets written specifically for patients and the public to explain and understand NICE guidance to help them decide whether to agree (consent) to the procedure or not. They give information on how well the procedure works and the risks and possible problems associated with it. They suggest questions to ask such as what are the risks associated with the treatment offered, what are the possible adverse events, and the pros and cons of having the treatment.

The guidance is available on the NICE website www.nice.org.uk.

Stress urinary incontinence

The main relevant NICE clinical guideline for SUI which has been recently updated is:

CG171 – Urinary incontinence: The management of urinary incontinence in Women Sept 2013 (update of CG40 2006).

This explains the treatment options available for urinary incontinence. It states that if lifestyle changes and pelvic floor muscle exercises are not successful, surgery may be suggested to treat SUI, which includes the surgical option of synthetic mid-urethral tape procedures.

There is also Interventional Procedure Guidance 'IPG262 Single-incision sub-urethral short tape insertion for stress urinary incontinence in women' 2008.

Pelvic organ prolapse

There are various surgical procedures involving mesh for treating pelvic organ prolapse and there are NICE patient information leaflets for 6 of these. Each leaflet gives information about:

- the treatment
- questions to ask their doctor, such as what risks and benefits of the procedure are and,
- what happens if something goes wrong.

Infracoccygeal sacropexy using mesh for uterine prolapse repair (IPG280)

Infracoccygeal sacropexy using mesh for vaginal vault prolapse repair (IPG281)

Insertion of mesh uterine suspension sling (including sacrohysteropexy) for uterine prolapse repair (IPG282)

Sacrocolpopexy using mesh for vaginal vault prolapse repair (IPG283)

Sacrocolpopexy with hysterectomy using mesh for uterine prolapse repair (IPG284)

Surgical repair of vaginal wall prolapse using mesh (IPG267)

They include information about the treatment, questions to ask their doctor such as what the risks and benefits of the procedure are. There are brief summaries of the possible risks and benefits of the procedures based on published studies associated with these procedures; information on how well the procedures work, and information on the risks and possible problems that can occur giving percentages.

5.2.4 Professional clinical associations and colleges

[BAUS](#) – patient information leaflets available on their website, including: Sling procedure for Urinary Incontinence – female.

[BSUG](#) – several Patient Information Leaflets are available on their website, for example: 'an operation for stress incontinence Tension free vaginal tap TVT BSUG F2'; 'Suspended Mesh Kit Anterior Prolapse Repair – MESH AR BSUG F2.

[RCOG](#) – has several Patient Information Leaflets available on their website, including information on: pelvic organ prolapse and surgery for stress incontinence.

5.3 Guidance for clinicians on using vaginal mesh implants

5.3.1 Introduction

Clinical disciplines who are involved in surgery for vaginal mesh implants include: urology, urogynaecology and gynaecology. The first source of information for a clinician considering implanting a vaginal mesh implant would be the manufacturer's instructions for use (IFU) and any associated necessary training needed.

MHRA has website pages on vaginal mesh implants for SUI and POP aimed specifically at healthcare professionals that include the published York Report (see Section 4.4.3) and guidance on reporting adverse incidents to MHRA and what types of incident to report. There are also various sources of guidance available to clinicians involved in surgery for vaginal mesh implants on precautions to take, appropriate patient selection and expected complication rates.

5.3.2 Information from vaginal mesh implant manufacturers

The Medical Device Regulations (see Section 2.1) require all manufacturers to provide IFUs for their devices to inform professional and clinical users how to use and apply their products safely. For example, IFU will include sections on the description of the device, indications, instructions for use, contraindications, warnings and precautions and adverse reactions.

They are also required to provide information on the expected patient complications and adverse events. Some manufacturers also run training courses for clinicians on how to implant their devices correctly and safely.

5.3.3 NICE guidance

NICE 'interventional procedures guidance' advises the NHS on when and how new procedures can be used in clinical practice. It makes recommendations on the safety of a procedure and how well it works. Some guidance is written because the procedure is quite new which means there is not a lot of information yet about how well it works, how safe it is and which women will benefit most from it.

The independent experts who write the NICE guidance (advice) for the NHS include healthcare professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is, and ask the opinions of expert advisers.

The guidance is available on the NICE website www.nice.org.uk.

Related to stress urinary incontinence

The main NICE guidance associated with SUI is 'CG171 – Urinary incontinence: The management of urinary incontinence in women – Sept 2013' (an update of CG40 2006). This is a NICE clinical guideline that includes 'interventional procedure guidance' on surgical treatments for stress urinary incontinence including those involving synthetic mid-urethral tape procedures.

The recommendations cover: Assessment and investigation and various therapies and treatments available of which one is 'Surgical approaches for SUI' which includes 'synthetic tapes'. It also includes guidance on maintaining and measuring expertise and standards for practice.

The guidance in summary for using synthetic tapes is as follows:

'When offering a synthetic mid-urethral tape procedure, surgeons should:

- use procedures and devices for which there is current high quality evidence of efficacy and safety
- only use a device that they have been trained to use
- use a device manufactured from type 1 macroporous polypropylene tape
- consider using a tape coloured for high visibility, for ease of insertion and revision. **[new 2013]**

If women are offered a procedure involving the transobturator approach, make them aware of the lack of long-term outcome data. **[new 2013]**

Refer women to an alternative surgeon if their chosen procedure is not available from the consulting surgeon. **[new 2013]**

Use 'top-down' retropubic tape approach only as part of a clinical trial. **[new 2013]**

Refer to single-incision sub-urethral short tape insertion for stress urinary incontinence (NICE interventional guidance 262) for guidance on single-incision procedures. **[new 2013]**

Offer a follow-up appointment (including vaginal examination to exclude erosion) within 6 months to all women who have had continence surgery. **[new 2013]**

Information to facilitate discussion of risks and benefits of each suggested treatment for women with SUI is given in the form of a table (see Annex I) for post-surgery up to one year – for continence and perioperative events; and after one year – for continence, erosion, retention, voiding dysfunction and de novo overactive bladder symptoms.

The data show that up to one year post-operation, for procedures involving vaginal mesh implants for SUI, continence in the range of 60-90% is achieved, with peri-operative complications (e.g. erosion, retention, voiding dysfunction etc.) in the range of 1-12% depending upon surgical approach. More limited data at 10 years post-operation suggest that continence is still in the range of 56-85%, indicating that significant long-term benefits are achieved in the majority of women undergoing these procedures.

There is also Interventional Procedure Guidance 'IPG262 Single-incision sub-urethral short tape insertion for stress urinary incontinence in women' 2008.

This states that the current evidence on the safety and efficacy of these is inadequate in quality and quantity therefore this procedure should only be carried out in the context of research studies or through submission of data to a national register. The procedure should only be carried out by a clinician with specific training in this technique and systematic long-term follow-up is essential.

Related to pelvic organ prolapse

There are NICE guidelines for the following procedures associated with surgical treatment for pelvic organ prolapse.

Guidance is given for each procedure that includes current evidence on the efficacy and safety based on published research studies, and any special arrangements for clinical governance, consent and audit or research. Most of guideline documents give evidence on the efficacy and safety of the procedures but for most of the procedures they state that the evidence is inadequate in quantity and quality. The guidance documents do not state that the mesh should not be used but do state that mesh procedures should only be used with special arrangements for clinical governance, consent and audit or research.

For the following procedures NICE guidelines state that current evidence on the efficacy and safety is inadequate in quantity and quality. Therefore the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

- Infracoccygeal sacropexy using mesh for uterine prolapse repair (IPG280)
- Infracoccygeal sacropexy using mesh for vaginal vault prolapse repair (IPG281)
- Insertion of mesh uterine suspension sling (including sacrohysteropexy) for uterine prolapse repair (IPG282)
- Sacrocolpopexy with hysterectomy using mesh for uterine prolapse repair (IPG284)
- Surgical repair of vaginal wall prolapse using mesh (IPG267).

They state that for procedure:

- Sacrocolpopexy using mesh for vaginal vault prolapse repair (IPG283).

'current evidence on the safety and efficacy of sacrocolpopexy using mesh for vaginal vault prolapse repair appears adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and audit.'

The guidance for the various POP procedures gives evidence that for particular procedures vaginal mesh implants can offer significant improvements in failure rates compared with surgical repairs undertaken without the use of mesh. For example IPG 267 – Surgical repair of vaginal wall prolapse using mesh – reports failure rates of anterior repair of the vaginal wall (based on information from 10 RCTs) of 14 % with mesh, compared with 30% without.

5.3.4 Professional colleges, societies and associations

5.3.4.1 Royal College of Obstetricians & Gynaecologists (RCOG) and British Society of Urogynaecology (BSUG)

When the York Report was published by MHRA in 2012 (see Section 4.4.3), RCOG issued the following [position statement](#) in support of the report:

'Urinary incontinence and pelvic organ prolapse affect many women and can have an enormous impact on their day to day quality of life.

'Women seeking treatment for incontinence and prolapse should discuss all the options with their doctors including conservative non-surgical interventions. Surgical procedures can improve symptoms for certain women. However, women need also to know that any operation carries some risk whether with or without the mesh described in this report.

'The RCOG welcomes this report. It shows that adverse rates for vaginal tapes are quite low. For vaginal meshes the adverse rates are higher in some studies. It is important that clinicians adhere to the NICE guidelines and inform patients of the risks and benefits of any procedure.'

RCOG have informed us that they believe that expertise in the area of urogynaecology is fundamental to good decision-making. The promotion of products through so called 'early adopter surgeons' should be discouraged and high volume use, particularly of vaginal mesh implants, should alert the profession and regulators about potential poor decision making.

5.3.4.2 British Association of Urological Surgeons (BAUS)

There is guidance for the implementation of the NICE guidelines on the BAUS website:

<http://www.baus.org.uk/Resources/BAUS/Documents/PDF%20Documents/Sections/Female%20and%20Neurological%20and%20Urodynamic%20Urology/NICE%20guidance%20implementation%20guide%20final.pdf>

5.3.4.3 International Urogynecological Association (IUGA)

IUGA has published a guide for its members on classifying types of adverse events and problems that can occur with vaginal mesh implants.

On 21 July, 2014, IUGA released a [position statement](#) on mid-urethral slings (MUS) for stress urinary incontinence, which included the following statements:

'There is robust evidence to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use.'

'IUGA supports the use of monofilament polypropylene mid-urethral slings for the surgical treatment of female stress urinary incontinence.'

5.3.4.4 General Medical Council

It is not compulsory for clinicians to report adverse incidents to MHRA, but General Medical Council guidance published in February 2013 makes it clear that clinicians should report medical device

adverse incidents to MHRA, and make information available to patients about how they can report side effects. ([‘Good practice in prescribing and managing medicines and devices’](#)).

5.3.4.5 DH / NHS England

Nov 2012 – A letter was sent from Sir Bruce Keogh and Professor Keith Willet letter to NHS Medical Directors on vaginal mesh implants (Annex A) drawing attention to the publication of the York Report (see Section 4.4.3) and actions agreed by DH, the then NHS Commissioning Board, MHRA and the relevant professional associations to reduce the rates of adverse incidents with these devices. The letter also referred to NICE guidance, and an action plan of work to develop professional guidance.

Dec 2013 – Letter from Bruce Keogh (Annex B) co-authored by RCOG, BSUG, BAUS on ‘The surgical management of urinary incontinence and pelvic organ prolapse’. This pointed out the particular relevance of:

- using patient consent guidance currently available from specialist surgical societies
- the necessity to comply with NICE guidance for these procedures and the relevance of clinical audit
- the importance attached to reporting any adverse incidents to MHRA
- the need for surgery for mesh removal to be performed in specialised units.

The NHS England complex gynaecology clinical reference group (CRG) is developing specifications for the specialised commissioning of services for recurrent pelvic organ prolapse and recurrent urinary incontinence. The procedures required for further management of these problems will be provided by a small number of units which must meet specified criteria. This service will be funded through specialised commissioning, not Clinical Commissioning Groups. Service providers will only be funded if they meet the criteria set out in the specifications.

5.4 Reported legal action in the UK and worldwide

5.4.1 Legal action in the UK

MHRA is aware of at least two legal firms who are at the information-gathering stage of initiating class actions in the UK, one in Scotland and one in Wales.

5.4.2 Legal action in the US

Action was brought against Ethicon (a Johnson and Johnson company) in early 2013. The patient concerned was awarded damages and compensation relating to the surgical procedure, although no claims against the device itself were successful.

A landmark lawsuit in the United States, involving Ethicon and a member of the public, concluded at the end of February 2013. The patient was implanted with a vaginal mesh implant to treat POP, and had been forced to undergo multiple corrective surgeries. She was awarded \$7.76 million in punitive damages and \$3.35 million in compensatory damages. The jury found, by a majority verdict, that Ethicon failed to properly warn the patient's surgeon about risks associated with the device. However, the jury ruled that Ethicon did not defectively design the mesh and did not make fraudulent misrepresentations to the surgeon. Ethicon is appealing the decision.

In August 2013 a further case against CR Bard was successful. A jury found that the Bard Avaulta Plus Posterior BioSynthetic Support System was defective and that the company failed to provide adequate warnings of the risks of the device. A high number of lawsuits are now in process in the US.

There are approximately 2,000 other lawsuits waiting to go to trial in the US, involving Ethicon alone. Other manufacturers who have lawsuits taken out against them or have settled out of court include CR Bard and AMS.

In April 2014, a Texan Jury ordered J&J (Ethicon) to pay \$1.2 million, in compensatory damages, to a woman implanted with a TVT-O mesh sling. The jury concluded that the design of the device was flawed. However, the Jury rejected the woman's claim that Ethicon didn't provide proper warnings about the slings' health risks and declined to award punitive damages. Ethicon are planning to appeal the compensatory damages awarded.

In September 2014, Endo International Plc reached agreements to settle up to 20,000 legal claims from women who said they were harmed by vaginal mesh implants, ending nearly all of the U.S. cases against it and its American Medical Systems unit. The company did not admit liability, but did increase the amount of money it had set aside to cover claims from \$1.2 billion to approximately \$1.6 billion.

5.4.3 Legal action in Australia

In October 2012, a case was launched that was reported to become the largest product class action in Australian legal history. Involving Johnson & Johnson, it was the company's third class action in Australia in as many years. It was being fought on behalf of a group of women who suffered devastating side-effects from what was supposed to be a simple medical procedure to treat prolapse after child birth.

5.5 Media activity

5.5.1 UK-wide media interest

Radio – Vaginal mesh implants has been discussed in a few BBC radio programmes.

Radio 4: Jan 2012 a patient representative talking about her problems and bad experience with TVT

May 2013 – 'Woman's Hour' May 2014

Jan 2014 – 'Face the Facts'

April 2014 – 'You and Yours' discussed the need of a register for all those who have undergone mesh implants. MHRA provided input.

Television – In May 2014, Channel 4's 'Embarrassing Bodies – Live from the Clinic' featured a woman who had a positive impact to her life following insertion of a mesh implant to treat stress urinary incontinence.

Answers were provided to questions from the Newsnight Research team on 27 March and 3 April 2012 on vaginal mesh and tapes. However, no programme has featured yet.

Print and internet – occasional articles about vaginal mesh implants in The Independent and The Telegraph.

The Daily Mail has featured a few case report type articles focussed on individual women. For example, in August 2011 they featured an individual lady with TVT, who says it has ruined her life and now suffers from constant pain and infections. In Dec 2013 they had an article: 'Victory for the Mail on surgery that left thousands in agony: Hospitals ordered to warn patients over incontinence operation that can go cruelly wrong'.

An investigative journalist for The British Medical Journal (BMJ) has asked MHRA several questions but no article has been published yet

5.5.2 Scottish media interest

Although there has been some media interest by other Scottish publications such as The Scotsman, the Daily Record/Sunday Record began running a campaign from early 2013. A journalist for the newspaper also gave evidence to the Scottish Petitions Committee on the 3rd June 2014 (see Section 5.6.1)

From early 2013 to mid-2014, the Daily Record/Sunday Record published approximately 35 articles on an almost weekly basis, beginning on 24 March 2013. The article reported that hundreds of Scottish women could be suffering horrendous health problems because of plastic mesh used to treat prolapse and bladder problems. The reporter knew of at least 15 women who were 'taking legal advice on compensation claims as experts say the problems could be more widespread than those in earlier scandals surrounding hip transplants and PIP breast implants.'

BBC Scotland, then BBC Health pages reported on the Scottish Health Secretary Alex Neil's decision and press statement about advising Health Boards to consider suspending the use of mesh. On 22 June 2014, the Daily Record/Sunday Record published an article with the headline, 'Alex Neil: I chose to suspend mesh surgery ops because I did not trust official figures'.

In early October, an article titled, 'Revealed: Two doctors on mesh safety review team linked to makers of controversial devices' questioned possible conflicts of interests of two clinicians who form part of the Scottish Independent Review group.

5.5.3 International media interest

New Zealand

Media reports appear to have started around 2012 indicating that health authorities backed the use of vaginal mesh implants. Case stories of affected women were featured and a support group created called 'Mesh Down Under'. More recent media has centred on campaigners from Mesh Down Under presenting a petition to the New Zealand Health Select Committee.

Australia

Reports have been on issues related to vaginal mesh implants including: class actions and individual case stories of women claiming to be severely affected by mesh surgery 'it felt like barbed wire scratching the inside of her body'. 390 women, at the time had signed up to the class action against Johnson & Johnson.

Canada

Reports started around mid-2012. The main focus is about women wishing to have the implant removed, to be given funding to have the procedure in the United States where there are suitably qualified surgeons.

5.6 Scotland

5.6.1 Summary of recent actions

MHRA has been working very closely with our counterparts, including the deputy Chief Medical Officer, in the Scottish Government for the past three years on issues raised with vaginal mesh implants. They have been copied into all UK Government Ministerial briefings and there has been regular exchange of information.

Since early 2013, there has been sustained media interest and campaign group activity on complications associated with vaginal mesh implants. The Scottish Government set up a Transvaginal Mesh Working Group, including patient representatives in 2013.

A Public Petitions Committee hearing was set up to hear evidence from affected women on 3 and 17 June 2014.

MHRA have responded to two letters from Alex Neil, Scotland's Cabinet Secretary for Health and Wellbeing, expressing concerns about vaginal mesh implants, and he has met with the MHRA Chairman and Clinical Director of Devices.

On the 17 June 2014 after the 2nd Public Petitions Committee hearing, the Scottish Government issued a press release stating that Alex Neil had requested the Scottish Chief Medical Officer (CMO) to write to Scottish Health Boards asking them to:

'...consider suspending the use of synthetic mesh products in surgery for pelvic organ prolapse and stress urinary incontinence...'

Health Boards were also informed that an independent review would be set up in Scotland to report on issues raised in relation to transvaginal synthetic mesh implants.

They anticipate that this review will report early in 2015 and will take into account the findings of SCENIHR on 'The safety of surgical meshes used in urogynecological surgery' (report expected in January 2015). MHRA contacted the Scottish Government on 17 June asking them to provide any new evidence they had to support this change in policy. The deputy CMO responded saying that the Cabinet Secretary felt he needed to act to respond to the petition – this was not on the basis of new evidence, rather concern about the fact that we do not truly understand the incidence of complications as a result of underreporting and inability to track and comprehensively follow up women who have received implants.

5.6.2 Professional clinical reaction to recent Scottish action

A letter from **RCOG** and co-signed by **BSUG**, **EUGA** (Professor Linda Cardozo) and **IUGA** sent to all their members (Annex D) in June 2014 referred to the Alex Neil request and stated:

"The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing has changed since a letter was sent out to all practitioners before Christmas from Bruce Keogh, co-signed by myself."

Dr David Richmond, President, Royal College of Obstetricians and Gynaecologists

BAUS wrote to all their members (see Annex E) in June 2014 referring to the Alex Neil decision and saying:

'The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing had changed since a letter was sent out to all practitioners in December 2013 from Sir Bruce Keogh.'

The **Scottish Pelvic Floor Network (SPFN)** – a group of clinicians and surgeons – wrote to their members (see Annex F) stating:

'In line with the National Institute of Clinical Excellence Guideline CG171, the Management of Urinary Incontinence in Women, the SPFN supports the use of Synthetic Mid-Urethral Slings in surgical treatment of stress urinary incontinence in women wishing to proceed for surgical treatment after failure of the conservative treatment options. The SPFN also supports the current credible medical research in this field.'

On the 18 August 2014, the Chartered Society of Physiotherapy (CSP) issued a press release in response to the Scottish Action and Independent Review, [requesting an urgent meeting with the Scottish Government](#):

In the press release, CSP stated that they were concerned that many women will have to cope with the distressing symptoms of incontinence while the review is completed.

Professor Karen Middleton, chief executive of CSP said:

“It is essential that women suffering with incontinence or prolapse receive the support and care that they need. With the current hiatus over surgery there is a real danger that waiting lists will grow and become unmanageable and that this will result in misery and distress for patients. At the very least any savings from the suspension of surgery should be diverted into supporting the needs of these women.”

5.6.3 Scottish Health Board’s reaction to recent Scottish action

NHS Scotland consists of 14 regional NHS boards. From media reports, MHRA is aware that several of the health boards said they would agree to the health secretary’s request in the Scottish CMO’s letter, while a few said that they had not used the procedure in a while.

NHS Dumfries and Galloway were reported to have stated:

“NHS Dumfries and Galloway has not carried out mesh procedures for pelvic floor reconstruction for some time and we do not plan to undertake this surgery in the foreseeable future.”

NHS Fife associate medical director Dr Gordon Birnie was reported to have said:

“NHS Fife has not used mesh for the treatment of pelvic organ prolapsed for a number of months, although the material has still been used for tension free vaginal tape procedures. However, in light of the publicity surrounding the health secretary’s announcement, we have taken a decision to postpone all such procedures until further notice.”

6 Risk–benefit analysis

Key points

- risk is defined as a combination of the probability of occurrence of harm and the severity of that harm
- the perception of risk–benefit balance varies for different patients, the general public, healthcare professionals, manufacturers and from a regulatory standpoint
- according to the first essential requirement of the Medical Device Directive, manufacturers are required to design and manufacture medical devices in such a way that, when the devices are used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient
- data for vaginal mesh implants for SUI indicate that the overall benefit outweighs the relatively low rate of reported complications
- given the benefits seen with vaginal mesh implants for POP, the overall benefits appear to outweigh the risks. However, further work is needed to characterise long-term safety in relation to different surgical procedures and vaginal mesh types.

6.1 Risk

Risk can be sub-divided into two components:

- the probability of occurrence of harm
- the consequences of that harm, that is, how severe it might be.

These concepts may be very subjective when viewed from an individual perspective. However, decisions on the benefits and risk management of medical devices will involve the collaboration of people and organisations such as:

- patients and members of the public
- clinicians and the organisations providing health care
- government/MHRA
- industry.

Statements about risks will have a different meaning from a regulatory standpoint when compared to interpretation by individual patients, patient groups, the general public and healthcare professionals with regard to medical devices. The regulatory view of risk should take into account the available evidence and be regularly reviewed in the light of new evidence.

Patients are at the heart of any risk assessment about treatment decisions. The patient decides on the treatment option that is best for them following a discussion with their physician.

The clinician should be aware of the known relative risks associated with a particular procedure or device supplemented by their own knowledge, skills, training and experience. In addition, the surgeon has the information from the manufacturer in the instructions for use (IFU) for the device. These instructions will include the output from the manufacturer's own risk assessment including: contraindications, relative contraindications for use and the potential complications associated with the use of the device. The clinician will be aware of what is not known about the procedure, particularly when new techniques intended to improve patient outcomes are being introduced.

Vaginal mesh implants are permanent implants that are not designed to be removed. Some contain degradable components, such as a coating, but they are likewise not meant to be removed. Risk assessment is, therefore, not a static concept – risk assessment will evolve throughout the lifetime of the device. The risk assessment made before the medical device was inserted will evolve and change during the perioperative and post-operative phases. Short-term and longer term outcomes will further affect the ongoing risk assessment.

6.2 Definitions

The most commonly used risk management system in medical device regulation is described in the international standard: ISO EN 14971:2007 Medical devices – Application of risk management to medical devices:

Harm – physical injury or damage to the health of people, or damage to property or the environment

Hazard – potential source of harm

Risk – combination of the probability of occurrence of harm and the severity of that harm

Risk analysis – systematic use of available information to identify hazards and to estimate the risk

Risk assessment – overall process comprising a risk analysis and a risk evaluation

Safety – freedom from unacceptable risk

Risk management – systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk.

There is no definition of benefit within the standard. The European Commission guidance document on clinical evaluation for medical devices (MEDDEV 2.7.1 rev 3) discusses risks and benefits in terms of the benefits that are intended by the device manufacturer. These will be outlined in information provided by the manufacturer.

6.3 Intended benefits

The intended benefits for the device are normally very simply stated in manufacturer's IFU and are similarly stated in the Scottish Patient information leaflet. Vaginal mesh implants are intended to be used to treat either SUI, or POP.

6.4 Reported harms

The type of patient harm resulting from vaginal mesh implant surgery is apparent from adverse incident reports to MHRA and NRLS. There is also evidence from correspondence with patient support groups. Published research literature indicates the most prevalent reported types of patient harm.

The most commonly reported harms include (also see Section 4.1):

- post-operative pain
- sexual difficulties
- vaginal erosion
- need for reoperation
- organ perforation.

6.5 Potential harms

A manufacturer's IFU includes sections on the description of the device, indications, instructions for use, contraindications, warnings and precautions and adverse reactions.

Potential adverse reactions listed by the manufacturer include:

- erosion
- inflammation
- urinary tract obstruction
- vaginal extrusion
- migration
- fistula formation.

Risks of surgical procedures listed by the manufacturer include:

- puncture or laceration of vessels, nerves, bladder or bowel
- defective healing or wound dehiscence
- recurrent prolapse
- prolapse occurring in other compartments
- dyspareunia
- pelvic pain
- infection
- urinary incontinence.

6.6 Potential sources of harm

Factors that could be a potential source of harm in relation to vaginal mesh implant surgery include:

The material

Most of the devices are made of polypropylene, which is a polymer widely used in medical applications such as non-absorbable synthetic suture materials and in the repair of abdominal wall hernias. There is no current evidence to suggest that the use of this material in medical devices causes undue toxicological risk to patients. NICE guidance indicates that polypropylene is widely understood to be an inert material and when used as an implantable material generally elicits minimal host response.

The amount of polypropylene mesh in a vaginal mesh implant for SUI is much smaller than in that used for POP. However, both types of implant can still erode through vaginal mucosa and there can be failure of the vagina to heal over the mesh.

The physical design

Vaginal mesh implants are permanent implants that are not intended to be removed. They are generally made from non-absorbable polypropylene, derived from non-absorbable sutures, entwined in a woven or knitted mesh construction. The pore size within the mesh varies depending on the diameter of the polypropylene yarn/filament used and the construction method for the mesh. A larger area of mesh is used for POP repair than that used for treating SUI.

By using a mesh structure a layer of tissue can grow through the interstices (holes) of the mesh and incorporate into adjacent tissue in order to give strength to the repair. If a mesh structure was not used (e.g. a non-porous material) there would be too much movement of the device, even if the material was tied-in with sutures.

Patient related factors

NICE guidelines refer to factors that can be associated with vaginal mesh implant for SUI failure. These include, for example:

- mid-urethral closure pressure of 31cmH₂O or more

- BMI more than 35
- primary surgery vs secondary surgery
- pre-operative anticholinergic medication use.

Patients may have several other comorbidities which could affect the outcome of vaginal mesh implant surgery, while others may have none at all.

How the vaginal mesh implant is used

There are surgical risks associated with the procedure and these will vary according to which procedure is used and the final anatomical location of the mesh. Surgical and procedural risk factors will include those mentioned in the manufacturer's instructions. The knowledge, experience, skills and training of the surgeon are also a significant factor.

NICE guidelines say that surgeons should have experience for each type of vaginal mesh implant procedure. Experience of using particular devices with some procedures is recommended as requiring higher levels of clinical governance and audit. Surgeons would be expected to take the manufacturer's IFUs for the devices into account.

As with all surgical procedures, there is a developing level of expertise as the clinical community gains experience with the implantation of a particular device. This should be viewed on a background of understanding that the basic tenets of surgery remain across all of surgical practice so that although a component of the surgery may be new the principles of surgical technique are essentially the same.

The instructions for use (IFU)

Further hazards could arise where instructions for use are inadequate or do not keep up to date with information gained in the post-market phase.

6.7 Perception of benefit and risk for patients

From the perspectives of some women, the benefits of undergoing mesh implantation procedures have not outweighed the risks. It has been clear from reports and communications from women to MHRA, that some of them with SUI who led otherwise generally healthy and active lives before surgery, have experienced significant health problems subsequent to vaginal mesh implantation. Their post-operative perception of the benefits and risks associated with vaginal mesh implantation is likely to be very different to that of someone who underwent a successful POP procedure to treat a severe prolapse of her pelvic organs. Likewise, women who have experienced no significant problems with surgery for a vaginal mesh implant for SUI will have completely different perceptions of benefit and risk.

Perception of benefit and risk can vary greatly depending upon cultural background, the socio-economic and educational background of the society concerned, the actual and perceived state of health of the patient, and many other factors. The way a benefit or a risk is perceived also takes into account, for example, whether exposure to the hazard seems to be involuntary, avoidable, from a man-made source, due to negligence, arising from a poorly understood cause, or directed at a vulnerable group within society.

MHRA recognises that the perception of benefit and risk for patients and members of the public when considering treatment using medical devices will likely be very different to the interpretation of benefit and risk within the regulatory framework.

An individual's assessment of benefit and risk associated with a medical device will be dependent on the information available to them from their clinician, from any patient information leaflet they have been given and any other information they may have researched themselves. This will and should be interpreted in light of their personal medical condition and circumstances.

The NICE patient information leaflets for vaginal mesh implant surgery for SUI and the various surgical procedures involving vaginal mesh implants for POP (see Section 5.2.3) give information about each treatment option, questions to ask their doctor such as what the risks and benefits of the procedure are, are there any long-term adverse events, and what happens if something goes wrong.

For each procedure there are brief summaries of the possible risks and benefits based on published studies associated with these procedures, giving percentage outcomes of success and failure reported.

It is clearly stated in these patient leaflets:

‘You might decide to have this procedure, to have a different procedure, or not to have a procedure at all.’

NICE guidance is written by considering how well an interventional procedure works and how safe it is, through asking the opinions of expert advisers. Their leaflets produced specifically for patients and the public (see Section 5.2.3) to explain and understand NICE guidance are to help them decide whether to agree (consent) to the procedure or not. These give information on how well the procedure works and the risks and possible problems associated with it. It suggests questions to ask such as what are the risks associated with the treatment offered, what are the possible adverse events, and the pros and cons of having the treatment.

6.8 Perception of benefit and risk for clinicians

Even if every conceivable safety measure is performed there will always remain an element of ‘risk’ associated with the use of medical devices, however small. This is commonly referred to as residual risk.

For clinicians, the decision to use a medical device in a particular clinical procedure requires the residual risks to be balanced against the anticipated benefits of the procedure for any given patient or group of patients.

Such judgments should take into account the intended use and location of a medical device, the performance and risks associated with the medical device, as well as the risks, benefits and uncertainty associated with the clinical procedure or the circumstances of use. Some of these judgments can be made only by an appropriately qualified medical practitioner using their knowledge, skills, training and experience.

Clinical judgement by a consultant clinician will take into account information about the risks, benefits and uncertainties associated with the use of the device and knowledge of the state of health (co-morbidities) of an individual patient and the patient’s own informed opinion.

The clinical community forms a perception of ‘risk’ from their own clinical training and experience, continual review of literature and from the IFU for vaginal mesh implants provided by the manufacturer. Clinicians have a responsibility to understand the use of the device and known risks, such as what can go wrong and how to mitigate against these. They should take account of any guidelines in place.

NICE guidance is very clear about the need to discuss the risks and benefits with patients. They state that their guidance represents the view of NICE, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics.

NICE ‘interventional procedures guidance’ (see Section 5.3.3) advises the NHS on when and how new procedures can be used in clinical practice. It makes recommendations on the safety of a procedure

and how well it works. Some guidance is written because the procedure is quite new which means there is not a lot of information yet about how well it works, how safe it is and which women will benefit most from it, for example this applies to : 'IPG267 Surgical repair of vaginal wall prolapse using mesh'.

They state that some recommendations can be made with more certainty than others. Their Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. The wording used in the recommendations denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.

The patient information leaflets available from the professional associations (see Section 5.2.4) also give information on the risks and benefits associated with vaginal mesh implant surgery and expected adverse events. For example, the BAUS leaflet for SUI vaginal mesh implants lists expected adverse events in terms of 'Common (greater than 1 in 10)' or 'Occasional (between 1 in 10 and 1 in 50)'. They do not list any adverse events as 'Rare (less than 1 in 50)'. They give information on how they calculate risk analysis for surgical outcomes taking account of patient variations such as age, sex, and number of other illnesses they have (known as co-morbidities). Some patients may have complex problems and others may have far fewer, which also needs to be taken into account.

The clinical community is supportive of the continued use of vaginal mesh implants for SUI as demonstrated by public statements from RCOG, BSUG and IUGA (see Section 4.6). They have also indicated that use of vaginal mesh implants for POP should be continued provided all the appropriate cautions and clinical governance are adhered to.

6.9 Perception of benefit and risk for manufacturers and notified bodies

According to the first essential requirement of the Medical Device Directive, manufacturers are required to design and manufacture medical devices in such a way that, when the devices are used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients provided that any risks which may be associated with their intended use constitute acceptable risks when weighed against the benefits to the patient.

All of the vaginal mesh implants are CE marked, and the majority are Class IIb medical devices in Europe.

To ensure that manufacturers have complied with these requirements a notified body (see Section 2.1.5) will have sampled across the range of a manufacturer's products and processes. The manufacturer's technical files will also be sampled which will include a review of the risk management file.

6.10 Conclusions on benefit and risk

In considering the overall risk–benefit balance of vaginal mesh implants for SUI no one conclusion is given as to how successful the treatment option is, as this will depend on different surgical approaches.

However, within the recommendations of the NICE guideline CG171 for management of urinary incontinence in women (see Section 5.3.3) information is given to facilitate discussion of risks and benefits of treatments for women with SUI. This is in the form of a table (see Annex I) for each procedure of risks and benefits up to one year – for continence and perioperative events; and after one year – for continence, erosion, retention, voiding dysfunction and de novo overactive bladder symptoms. The data show that up to one year post-operation, for procedures involving vaginal mesh implants for SUI, continence in the range of 60-90% is achieved, with peri-operative complications (e.g.

erosion, retention, voiding dysfunction etc.) in the range of 1-12% depending upon surgical approach. More limited data at 10 years post-operation suggest that continence is still in the range of 56-85%, indicating that significant long-term benefits are achieved in the majority of women undergoing these procedures. Thus the overall benefit outweighs the relatively low rate of complications.

In considering the overall risk–benefit balance of vaginal mesh implants for POP, the data on outcomes are more varied, reflecting the various procedures currently used.

NICE guidance for the various POP procedures does give evidence that for particular procedures vaginal mesh implants can offer significant improvements in reducing failure rates compared with surgical repairs undertaken without the use of mesh. For example IPG 267 – Surgical repair of vaginal wall prolapse using mesh – reports failure rates of anterior repair of the vaginal wall (based on information from 10 RCTs) of 14 % with mesh, compared with 30% without.

Most of the POP guideline documents give evidence on the efficacy and safety of the procedures but for most of the procedures they state that the evidence is inadequate in quantity and quality. The guidance documents do not state that the mesh should not be used but do state that mesh procedures should only be used with special arrangements for clinical governance, consent and audit or research.

The types of adverse incident, reported in the York report from research published up to 2012, associated with the use of vaginal mesh implants for these procedures are: post-operative pain/discomfort; erosion; deterioration in sexual function, need for re-operation and organ perforation. According to the York report, these events occur with a frequency of, on average, 6.5% or below, with the exception of deterioration of sexual function, which occurs on average in 15.3% or below of subjects.

Given the benefits seen, the overall benefits appear to outweigh the risks, but further work needs to be done to characterise long-term safety in relation to different surgical procedures and mesh types. We will propose that this work should be considered by the NHS England led working group, recognizing that research is already underway as part of the PROspect trial (see Section 8.4.1).

7 Discussion

7.1 Background

The first indications of a possible increase in risk associated with vaginal mesh implants came to light around 2010 when MHRA started receiving correspondence from individuals and patient groups saying that they had suffered from severe complications. These included cases of debilitating, persistent pain, sexual difficulties and erosion of the vaginal mesh implant through vaginal tissue. It was not clear how prevalent these problems were and whether they were due mainly to the surgical procedure, the vaginal mesh implant or any other factors. Therefore, MHRA launched an investigation to better understand the use of these devices and the complications associated with their use.

7.2 Assessment by the MHRA within the regulatory framework

MHRA review of notified bodies

All vaginal mesh implants are CE marked, and the majority are Class IIb medical devices, which means a notified body will have sampled across the range of a manufacturer's products and processes to ensure that the essential requirements of the Medical Device Directive are being met. The manufacturer's technical files will also be sampled which will include a review of the risk management file. This is very different to pharmaceutical products where the competent authority performs the pre-market assessment of products.

All European notified bodies for medical devices are in the process of, or will be re-designated to ensure they are working to the same required standard.

Conformity assessment tasks are conducted by the notified body. MHRA is not involved in the routine review of the manufacturer's pre-market risk assessments. However, during our continuous monitoring of the performance of notified bodies, we sample their work and review their files to ensure compliance with the requirements.

Our review of information provided by one of the UK notified bodies known to have assessed several of the vaginal mesh implants widely used in the UK, confirmed that there are no major concerns with the risk/benefit assessment undertaken by the manufacturers.

7.3 Post-market surveillance of vaginal mesh devices

Vaginal mesh devices are soft tissue implants that are intended to have many years of use inside the human body and, therefore, there are limitations to what can be studied pre-market, such as animal models. Adverse incidents could be related to sporadic manufacturing defects in components, operator-dependent variations in implantations, and long-term failure related to mechanical or chemical processes in the human body.

It is not feasible to adequately study the absolute long-term safety and performance of any implant in patient groups of sufficient size and diversity prior to their being placed on the market. Ongoing post-market surveillance of implants is therefore a particularly critical aspect of the regulatory system for these devices. Manufacturers, notified bodies, clinicians, patients and regulatory authorities all have an important role to play in the operation of an effective post-market surveillance system.

Adverse incident reports

The number of adverse incident reports received by MHRA and NRLS has been very few when compared to the number of implants indicated to be in use in the UK. In a context of under-reporting, we do not believe that vigilance data give the full picture about device safety.

Although we acknowledge there is under reporting of adverse incidents to MHRA, if there was an inherent safety problem with vaginal mesh, we would expect to see a far greater proportion of adverse incident reports from clinicians as well as from affected women.

When compared to the denominator figures available to us, such as manufacturer sales figures and HES data (England) on how many mesh devices are implanted, it suggests that the majority of women who have this surgery experience little or no long-term problems.

Although the number of adverse incident reports that MHRA has received has increased since 2011, stimulated we believe by the raised awareness of issues, in comparison to the sales figures, they are still relatively very few. Adverse incident reports will also relate to vaginal mesh implants that have been implanted at any time over the last 10 years. Sales figures for the UK indicate that the number of SUI vaginal mesh implants used peaked in 2009 from about 21,500 and is now fairly stable at around 17,000 per year. The number of POP vaginal mesh implants used peaked around 2009 with 3,200 sold and has now dropped gradually to about 2000 per year.

Some women have alleged that the vaginal mesh implant becomes brittle over time and shrinks within the body. However, we have seen little evidence of this from adverse incident reports, published literature and MHRA enquiries to manufacturers.

There have also been allegations that the polypropylene leaches 'dangerous chemicals' into the body. However, an important part of a manufacturer's compliance with the essential requirements is the need to carry out a full biological safety risk assessment of the materials used in the device. In this risk assessment, consideration is given to all toxic endpoints including possible adverse immune reactions while implanted. Polypropylene is a material that is widely used in medical applications apart from vaginal mesh implants such as in non-absorbable synthetic suture materials and in the repair of abdominal wall hernias. MHRA does not have evidence to suggest that the use of this material in medical devices causes undue toxicological risk to patients.

Denominator data

HES data are only available for England, and assuming that the HES coding has been correctly applied, HES indicates that a total 100,811 vaginal mesh implants for SUI were implanted between 2005 and 2013. There are figures indicating that 4,025 vaginal mesh implants for SUI have been removed in that period. However, we cannot assume that these indicate there has been a problem with the mesh or that the patient has suffered harm. There can be several different clinical reasons for removal of the implants which could include partial trimming of the mesh erosion post procedure.

HES data indicate that 8,296 vaginal mesh implants for POP were implanted between 2006 and 2012, which is considerably less than the number of vaginal mesh implants for SUI used. There are no HES figures that indicate vaginal mesh implants for POP removal surgery. NICE guidance for POP procedures with mesh which have been in place since 2008/9, strongly states that they should only be used with special arrangements for clinical governance, consent and audit or research. This may explain why the UK does not appear to have as many adverse incidents associated with vaginal mesh implants for POP compared to the United States.

Literature

There are many articles published in the professional literature about the performance of vaginal mesh implants. The focus of the York report was on peer reviewed literature based on Randomised Controlled Trials (RCTs) where possible from studies which included more than 50 patients, because studies with fewer patients were not considered to be statistically robust.

The results did not indicate any significant concerns with vaginal mesh implants used for SUI and are consistent with the evidence used for the NICE guidance for treatment of SUI with vaginal mesh implants – which has recently been updated in 2013.

There was some higher percentage complication rates recorded for vaginal mesh implants for POP, in particular for pain associated with sexual intercourse. However, it is important to note that these devices were introduced to reduce the high failure rates associated with previous surgical techniques.

Many women with incontinence or prolapse have considerable sexual problems prior to surgery, and for many of these women the symptoms are improved following surgery.

We recognise there is a lack of long-term research data available for some of these devices. Many have been available on the market for less than 20 years. Research on the long-term effects such as after 10 years is just starting to be published.

The York Report review of literature is two years old. NICE guidance CG171 on the management of urinary incontinence in women was recently updated and published in 2013 and refers to recently published articles. We also anticipate that SCENIHR will review the most recent literature as part of their ongoing work (see Section 8.4.4).

Patient experience

MHRA have taken full account all the information provided to us by patients and patient group representatives. It was mainly due to their concerns expressed that MHRA first initiated an investigation into vaginal mesh implants, especially as the number of adverse incident reports we received were so few.

Many adverse incidents reported by patients have been consistent with those reported in the research based literature. Other indications reported by a few patients as being caused by vaginal mesh implants have not been verified by clinical opinion, for example: blurred vision or fibromyalgia.

In addition to adverse incident reports, individuals and patient groups have provided general information to MHRA. This included copies of FDA publications and published articles in professional journals. Some information MHRA has not been able to consider as robust evidence, such as newspaper articles, reports of court cases, photographs from YouTube videos.

However, some of the information provided to us has indicated other areas of concern associated with the use of vaginal mesh implant surgery that are outside of MHRA's remit, such as lack of comprehensive informed patient consent and lack of awareness of possible complications that are expected to occur from vaginal mesh implant surgery. There have also been indications that there may be a lack of knowledge amongst some GPs and clinicians about what types of adverse events may occur.

The MHRA fully recognises that there is little systematic collated information available about patient experience of surgical implantation of these devices, and there appears to be little available evidence of long-term clinical follow up. The only outcomes we are typically made aware of are from those individuals who have experienced adverse effects.

Clinicians

The clinical community in the UK and worldwide have indicated that are that they support the continued use of vaginal mesh implants for SUI. The relevant professional associations and Royal Colleges have made public statements to this effect; many in response to the recent Scottish Government announcement asking Health Boards to consider suspending the use of vaginal mesh implants for both SUI and POP. They have also been cosignatories with Sir Bruce Keogh for letters to the NHS stressing the importance of: following NICE guidance on the surgical procedures associated with SUI and POP; regular audit; reporting adverse events to MHRA; specialist surgery for removal of vaginal mesh implants.

Information from manufacturers

As part of MHRA's review of vaginal mesh implants, information regarding post-market surveillance procedures held by the seven main manufacturers was reviewed. It contained comprehensive literature reviews, post-market surveillance data, vigilance, clinical trial data and risk conclusions. The information was found to be consistent with that which has been separately reported by a sampled notified body and met with the relevant requirements for class IIb devices under the current legislation.

This sample covered the largest European notified body and the three manufacturers with the worldwide largest market share of tapes and meshes sales used in this type of surgery.

EU and worldwide

MHRA monitors activities, worldwide, related to vaginal mesh implants. We are not aware that any other country worldwide has seen sufficient evidence to take any enforcement action under their regulatory system against any manufacturer in relation to vaginal mesh implants.

MHRA has not carried out any enforcement action related to vaginal mesh implants and is not aware of any other CA in the EU doing so, at the present time. Although it is feasible that a Member State may not share information regarding a particular enforcement action with other Member States; MHRA understands that this would be a rare situation, given the fact that the products, once CE marked can be placed across the EU without further restrictions.

All the legal action we are aware of has been by individuals against clinicians and manufacturers.

The FDA is proposing to reclassify vaginal mesh implants for POP from Class II to Class III, under US regulation. It should be noted that the United States classification system for medical devices is not equivalent to the EU classification system. Therefore, a similar change in classification in the EU will not have an equivalent effect. In the EU vaginal mesh implants are already classed in the medium to high risk category.

Enforcement action

The safety and performance of medical devices is monitored using clearly defined concepts and processes in regulation. Appropriate risk management, requires close collaboration of regulators such as MHRA, with notified bodies and manufacturers.

MHRA is responsible for ensuring that all medical devices placed on the UK market are compliant with the relevant legislation and has a duty to enforce this legislation on behalf of the Secretary of State for Health. MHRA investigate all allegations of non-compliance and ensures that the appropriate action is taken whenever necessary to prohibit or restrict unsafe products being placed on the market and/or put into service.

In the event that a breach of the legislation is identified, any enforcement action taken by MHRA will be proportionate and risk based. Action may range from prosecution where there is a serious risk to public health, or for repeated non-compliance, to other forms of less noticeable compliance action where the product may remain on the market pending the corrective action. MHRA can also enforce suspension notices and prohibition notices to restrict, suspend or stop the supply of any devices which are considered to be unsafe or not in compliance with the regulations.

The MHRA has not had a robust body of evidence indicating that vaginal mesh implants are non CE compliant; to be able to initiate any enforcement action against any manufacturers in the UK under the European Medical Device Directive and, to the best of our knowledge neither has any other EU country.

7.4 Does the evidence indicate an increased risk?

As discussed in Section 6, we recognise that the statement 'the benefit outweighs the risk' may be interpreted differently from the regulatory view by individual patients, patient groups and healthcare professionals.

MHRA needs to take into account all the available evidence and can only regulate on the information that we have available, and all parties involved have to cooperate in providing relevant information. The regulatory system is based on mutual trust and cooperation with an emphasis on encouraging compliance.

From our review of the information available to us, there appears to be no evidence that vaginal mesh implants are non CE compliant that would justify MHRA taking enforcement action towards taking them off the market or removing them from use.

MHRA's current position is that for the majority of women, the use of vaginal mesh implants is safe and effective. However, as with all surgery, there is an element of risk to the individual patient. This conclusion is entirely dependent on compliance with the National Institute for health and Care Excellence (NICE) and other sources of guidance which emphasise the caution that should be exercised prior to surgery being considered. Whilst some women have experienced distressing and severe effects, the current evidence shows that when these products are used correctly they can help alleviate the very distressing symptoms of SUI and POP and as such the benefits still outweigh the risks.

However, we acknowledge that:

- a) benefit is difficult to quantify, and
- b) the final decision on risk/benefit at the individual level should be made by the woman following a discussion with a clinician.

Current NICE guidance for SUI and POP vaginal mesh implant surgery is very comprehensive with extensive information on the risks and benefits involved. However, our assessment of the information available indicates that further actions could be done to reduce the current rate of adverse incidents/harm experienced by individuals. These would include:

- improved patient selection
- informed patient consent.

It is also clear that there is a lot of information we do not have, such as comprehensive information on all patient outcomes. Suggested actions to address this could include:

- increased clinical audit
- long-term patient outcome measures
- patient reported outcome measures
- improved reporting of adverse incidents
- structured post-market clinical follow up
- use of a registry and/or Unique Device Identifier codes (UDIs).

8 Next steps

Key points

- MHRA is proactively working to improve reporting of adverse incident reports. This includes collaborative projects with NHS England such as Patient Safety Alerts and work with the National Reporting and Learning System (NRLS)
- in response to the Stephenson Review, MHRA has committed to continuing with the following; safety and performance monitoring, encouraging innovation, better collaboration with European partners and Unique Device Identifiers
- MHRA continues to negotiate with the EU on the proposed revisions of the MDD, to improve the regulatory framework for medical devices
- there are a number of working groups, projects and research exploring issues related to vaginal mesh implants. These include the NHS England led working group, the Scottish Independent Review, both of which we are actively involved in. Other groups we are engaged in include: the PROspect trial, the SIMS Trial, NICE Project and SCENIHR.
- MHRA is participating in the NHS England led Working Group, to identify any ways to address concerns with vaginal mesh implants and is involved in the Scottish Independent Review.

8.1 Introduction

MHRA is currently leading on various activities to improve the reporting of adverse incidents to MHRA, providing feedback to reporters, and making improvements to how we source and use clinical advice.

There are also a number of ongoing activities MHRA is aware of being undertaken by the NHS and other clinical bodies, specifically related to improving outcomes for patients from vaginal mesh implant surgery. MHRA involvement is to provide regulatory advice.

MHRA is aware of a number of ongoing research projects that are likely to provide useful information about the long-term safety and effectiveness of vaginal mesh implants.

8.2. Ongoing MHRA activities

8.2.1 Actions to improve adverse incident reporting in the UK

MHRA, NHS England and the Devolved Administrations have been working together on joint Patient Safety Alerts on improving reporting and learning.

Of particular significance has been MHRA's joint project with NHS England to improve medical device and medication error reporting. This project has involved engagement and feedback from a wide range of healthcare professional groups.

This stakeholder research has indicated that MHRA and NHS England need to make improvements in:

- the ease of reporting incidents to several organisations
- the local governance of medical device reporting and safety learning within healthcare organisations and,

- the amount of feedback from MHRA and NHS England to reporters.

8.2.2 Particular activity addressing ease of reporting and local governance

On [20 March 2014](#) MHRA, in partnership with NHS England, launched Patient Safety Alerts (PSA) relating to medical devices and medication errors respectively. These alerts gave the NHS and independent healthcare organisations six months (until 19 September 2014) to implement certain actions including:

- for large NHS organisations, such as acute Trusts, identifying board level oversight for patient safety such as a medical or nursing director
- identifying medication safety officers (MSOs) and medical device safety officers (MDSOs) who will be responsible for ensuring enhancements in the quantity and quality of patient safety incident reports
- identifying local networks to review patient safety incidents and reports and learning made via the National Reporting and Learning System (NRLS) and the MHRA
- participation was also invited from Clinical Commissioning Groups (CCGs).

MHRA and NHS England, as part of the above project, are working together with the National Reporting and Learning System (NRLS) to ensure that as soon as reasonably practicable, adverse incidents with medical devices and medication errors need be only reported to the NRLS, and the incidents would then be made available to MHRA with acceptable speed, content and quality to facilitate further investigation by manufacturers and MHRA.

MHRA and NHS England have also been piloting monthly WebEx sessions with MDSOs and MSOs designed to improve reporting, and encourage good patient safety practice at local level. These are getting good feedback and are providing valuable learning for how to run WebEx sessions with a full network post the full launch in September 2014.

To promote this initiative to the NHS and independent sector and ensure compliance with the PSA by September 2014, the project team have been exhibiting at key conferences and events. These have included: the Patient Safety Congress, the NHS Confederation, the RCN Congress and Patient Safety First (forthcoming).

In addition, MHRA has following research with similar stakeholders, concluded that the creation of a single brand for reporting to MHRA would be beneficial to reporters; particularly those in small organisations and members of the public. This work will deliver an easy to use Yellow Card branded MHRA reporting scheme to include issues related to medical devices, adverse drug reactions, defective medicines, and counterfeits.

8.2.3 Improving feedback to healthcare professionals and members of the public

MHRA has recently begun working with industry (via the Association of British Healthcare Industries) and representative clinical groups to try to improve the transparency of European Union (EU) medical device vigilance reporting through the introduction of a voluntary transparency scheme for industry.

User surveys have suggested that the current EU vigilance system enables far too little feedback on medical device events in the field, as reporters are keen to find out about similar medical device incidents with devices they either already use or are thinking of purchasing. Users consistently say that such an initiative would lead to improved levels of reporting by healthcare professionals in the future.

The scheme, as currently conceived, would involve industry agreeing for MHRA to release the full details of their final reports into the public domain. If the scheme were to become successful, it is likely that MHRA would develop a publicly available and searchable database, in a similar fashion to the Database of Adverse Event Notifications (DAEN) operated by the Australian Therapeutic Goods Administration (TGA). This work is currently a UK initiative only, but industry are keen for this issue to

be taken to Europe and MHRA have put it onto the agenda at the Vigilance Medical Device Expert Group.

8.2.4 Improving sourcing of clinical advice to MHRA

In response to the Stephenson review on sourcing clinical advice, MHRA has committed to the following:

- **safety and performance monitoring:** MHRA is building strategic partnerships with NHS England and equivalent institutions in the devolved administrations that will improve the flow of information about the safety and performance of medical devices. A network of Medical Device Safety Officers (MDSO) and Medicines Safety Officers (MSO) will drive continuous improvement within the NHS
- **encouraging innovation:** MHRA is committed to encouraging innovation and is working closely to address any problems identified with the regulatory framework and to engage directly with developers of new medical technologies through its Innovation Office that opened in 2013. For example, MHRA is committed to encouraging new stem cell therapies, genomics, regenerative medicines and new diagnostic software. Initial discussions have also been held with notified bodies in relation to using them to help identify new and innovative technologies which may challenge the regulatory system
- **better collaboration with European partners:** MHRA is continuing to build strategic relationships in Europe to strengthen the European regulatory system and the oversight of notified bodies. A number of common and joint working areas have been identified, these include improved processes and tools for post-market surveillance and work to develop EU IT infrastructure to underpin collaborative regulatory work
- **Unique Device Identifiers (UDI):** the MHRA recognises the value of UDI's in helping to monitor the safety and performance of implantable medical devices. The agency will work with the DH, NHS organisations, the Health and Social Care Information Centre (HSCIC) and the Clinical Practice Research Datalink (CPRD) to encourage NHS trusts to implement systems for UDI recording and analysis.

On the 18 of July, 2014, MHRA announced that a new independent Devices Expert Advisory Committee (DEAC) will be established before April 2015 and will be responsible for providing independent expert advice to MHRA. The new DEAC will replace the MHRA's current expert advisory group, Committee on Safety of Devices.

8.2.5 Revision of the Medical Devices Directives (MDD) – see Section 2.4

MHRA continues with negotiations with European countries on the revisions of the MDD to improve the regulatory framework for medical devices and consistency of working practices across Europe. The new MDD are expected to will include provisions for traceability and unique device identifiers, clearer rules on the use of clinical evidence and clearer responsibilities for manufacturers with post-market surveillance.

8.3 Working groups

8.3.1 Working group on vaginal mesh implants led by NHS England.

MHRA is participating in the NHS England led Working Group designed to establish the reasons for concerns from both the clinical and patient community regarding surgical procedures for POP and SUI using vaginal mesh implants, and identifies potential ways to address them. This is chaired by Professor Keith Willett, National Director for Acute Episodes of Care. It includes representatives from NHS England, DH, Scottish Government, and Welsh Assembly Government; along with the specialist societies, BSUG, BAUS and RCOG. Patient representatives are also present. The Northern Ireland Government have asked to be kept informed as work progresses.

This group first met on 16 July 2014 and we understand that some of the outcomes will include ongoing work looking at: improving data collection, better procedures for informed patient consent for example patient information leaflets. The next scheduled meeting will be held in November 2014.

8.3.2 Scottish independent working group

In June 2014, the Scottish Government Independent Review of transvaginal mesh implants was announced by the Scottish Chief Medical Officer (CMO) at the request of Alex Neil MSP. On 26 June 2014, it was announced that Dr Lesley Wilkie, a retired public health director, will lead the proposed independent review.

The first meeting was held on 25 August 2014 with Dr Neil McGuire, Clinical Devices Director, representing MHRA.

8.4 Other related on-going projects and research

8.4.1 PROspect

A DH funded PROspect trial on prolapse surgery involving vaginal mesh implants is due to be published in March 2016 with a draft report expected September 2015. To date, the Chief Investigator and research team have presented at conferences using some preliminary data comparing adverse effects in prolapse surgery. The draft report is not due until September 2015 and so it is still early for research outcomes to be published as a journal article. We would expect at least a clinical outcomes paper and an economics paper to be published as an output once the research is completed, as well as the full monograph which is due to be published in March 2016.

8.4.2 The SIMS trial

The SIMS Trial is a HTA funded (National Institute for Health Research Health Technology Assessment) randomised control trial (RCT) evaluating surgical and conservative treatment of urinary incontinence in women. This study is comparing the standard vaginal mesh implant for SUI with a smaller vaginal mesh implant, known as a mini-sling and will have a three year follow-up.

8.4.3 NICE project

NICE are running a project looking at looking at identifying procedure and device-related complications using routine information systems. One of the six different procedures being looked at is surgical operations involving the use of vaginal mesh implants.

8.4.4 SCENIHR

European Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) mandated for a scientific opinion on 'The safety of surgical meshes used in urogynecological surgery'. This is due to report back in January 2015.

9 Conclusion

- MHRA has reviewed currently available information on the safety of vaginal mesh implants and their use and has concluded that from a regulatory perspective the benefits of the use of these devices outweigh the risks. This means there is no justification for the MHRA taking regulatory action to remove all of these devices from use in UK hospitals.
- MHRA is not aware of any evidence that one manufacturer's device is significantly different from another manufacturer's device with regard to safety.
- MHRA will continue to keep available information about the safety of vaginal mesh implants under close scrutiny – in collaboration with NHS England and the relevant professional bodies – and will consider the need to take regulatory action or to issue further advice in the light of emerging evidence.
- MHRA proposes considering the following:
 - improved reporting of incidents
 - structured post-market clinical follow-up
 - registries or the use of unique device identifiers (UDIs)
 - Patient Reported Outcome Measures (PROM).

From:

Sir Bruce Keogh KBE, DSc, FRCS, FRCP
NHS Medical Director for England

Professor Keith Willett FRCS
National Clinical Director for Acute Episodes of Care,
National Commissioning Board



Gateway reference: 18412
21 November 2012

To: NHS medical directors

Dear Colleague

VAGINAL TAPES AND MESHES

This letter is to draw your attention to

- i the publication of a report from the Health Economics Consortium of York University on the rates of common adverse events associated with vaginal tapes (for treatment of stress urinary incontinence, SUI) and meshes (for pelvic organ prolapse, POP)
- ii the action agreed by the Department of Health, the NHS Commissioning Board, the MHRA and the relevant professional associations to reduce the rates of these adverse events;

and to ask you in the meantime to ensure familiarity with existing NICE and professional guidance on the safe and appropriate use of these devices.

NICE guidance

2. NICE's guidance on the use of vaginal tapes for stress urinary incontinence is set out in clinical guideline CG40. The guidance can be summarised as saying that these procedures can be recommended provided that

- conservative management has already been tried and is no longer effective
- surgeons have had specialist training and carry out a sufficient case load to maintain their skills
- surgery takes place under the oversight of a nominated clinical lead
- all surgeons should maintain audit data and contribute to national outcomes registries such as those maintained by the British Society of Urogynaecology (BSUG) and the British Association of Urological Surgeons (BAUS).

3. Guidance on the use of vaginal meshes for pelvic organ prolapse is set out in a series of interventional procedure guidance notes (IP 267, 280-284). NICE considers that, on the available evidence, surgical repair of vaginal wall prolapse using mesh may be more efficacious than traditional repair without mesh; however, the available evidence is limited in particular on longer term effectiveness and safety. NICE therefore recommends special clinical governance arrangements for most variants of these procedures.

The York University report

4. In the light of reported adverse events and concerns expressed by patient groups about vaginal tape and mesh procedures, the MHRA commissioned a report from the Health Economics Consortium of York University, reviewing the published literature on the most frequently reported adverse events. A summary table of the key findings is attached and the full report will be available on the MHRA website at either of the links in paragraph 6 below. In brief,

- adverse event rates associated with the various surgical techniques using vaginal tapes for SUIs are generally in the range 1-3% (9% for deterioration in sexual function for one technique);
- adverse event rates for surgical techniques using vaginal meshes for POP are in the range 2-6% for most outcomes, but 14-15% for deterioration in sexual function.

5. Interpretation of these findings is not straightforward; many patients were already experiencing symptoms such as sexual problems before surgery, and rates of adverse events for surgery not using implants are believed to be as high as or higher than those using implants. A current trial, the PROSPECT trial due to report in 2014, will give us evidence on the relative safety of prolapse repairs using native tissue repair and mesh implants.

Proposed action plan

6. In response to earlier concerns, the MHRA, working with the two professional associations – the British Society for Urological Gynaecology (BSUG) and the British Association for Urological Surgery (BAUS), has developed a range of materials for clinicians and patients, including patient information leaflets and a set of questions which patients should ask their surgeons when considering possible surgery. These will be available from tomorrow on the MHRA website at the following addresses:

Stress urinary incontinence:

<http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-M-T/Syntheticvaginaltapesforstressincontinence/index.htm>

Pelvic organ prolapse:

<http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-M-T/Vaginalmeshforpelvicorganprolapse/index.htm>

It would be helpful if these materials could be adapted locally as necessary for women who do not have English as their first language or who might have other difficulties in accessing them.

7. Building on this earlier work, DH, the NHS Commissioning Board, MHRA, and the professional associations have reviewed the findings of the York review, and have agreed the following action plan:

- To develop proposals for a single registry of vaginal tapes and meshes, building on the existing registries maintained by the professional associations;
- To develop and issue professional guidance for vaginal meshes, complementing existing NICE guidance, on aspects such as selection of patients, choice of device, and processes for informed patient consent;
- To develop and issue guidance to commissioners to encourage them to commission services from providers which maintain high standards of training and clinical audit;
- To develop and issue professional guidance on those centres competent to carry out surgery for women with recurrent problems from incontinence or prolapse, or women needing further surgery as a result of complications of tape or mesh surgery.

In addition, the review of cosmetic surgery which ministers announced in January 2012 is considering the possibility of developing outcomes registries for all high-impact medical devices.

Summary

8. We would welcome your support in making surgery using vaginal tapes and meshes as safe and effective as possible, and in reassuring patients that – appropriately used – they remain useful additions to the treatment options available for these distressing conditions. Any comments on this letter should be sent in the first instance to Charles Dobson (NHS Medical Directorate, Quarry House, Quarry Hill, Leeds LS2 7UE; charles.dobson@dh.gsi.gov.uk).

Yours sincerely



Sir Bruce Keogh
NHS Medical Director
Department of Health &
NHS Commissioning Board



Professor Keith Willett
National Clinical Director,
Acute Episodes of Care
NHS Commissioning Board

Summary table of the Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse

	Postoperative pain/discomfort after 6 months	Erosion	Deterioration in sexual function six months after operation	Need for reoperation on sling/tape/mesh	Organ perforation (POP only)
Incontinence surgery					
TVT / SPARC	0.0% (0.0% - 1.5%) Included studies = 3	1.1% (0.0% - 5.8%) Included studies = 24	9.3% (3.8% - 13.5%) Included studies = 3	0.9% (0.5% - 6.0%) Included studies = 6	N/A
TOT	0.9% (0.6% - 5.1%) Included studies = 4	2.4% (0.0% - 5.6%) Included studies = 25	2.5% (1.9% - 3.2%) Included studies = 2	0.0% (-) Included studies = 1	N/A
Single incision system	1.1% (0.0% - 1.9%) Included studies = 3	0.0% (-) Included studies = 1	No studies	No studies	N/A
		0.0% (-) Included studies = 1	No studies	No studies	N/A
Prolapse surgery: anterior/ posterior					
Synthetic non-absorbable	5.5% (-) Included studies = 1	6.5% (0.9%-19.6%) Included studies = 13	15.3% (12.8%-17.7%) Included studies = 2	4.8% (0.9%-10.9%) Included studies = 9	2.1% (0.9%-2.8%) Included studies = 4
Biological absorbable	2.7% (0.8%-7.5%) Included studies = 3	1.2% (0.0%-21.4%) Included studies = 7	No studies	3.2% (1.0%-5.4%) Included studies = 2	0.0% (-) Included studies = 1
Prolapse surgery: Uterine / vault					
Synthetic non-absorbable	2.0% (1.2%-2.3%) Included studies = 3	5.5% (0.0%-25.6%) Included studies = 31	14.5% (-) Included studies = 1	4.0% (0.8%-7.1%) Included studies = 12	1.8% (0.4% - 7.9%) Included studies = 16
Biological absorbable	No studies	No studies		No studies	No studies

Gateway reference: 00948

Ref: BK UI/POP1

To: Area Team and Regional Medical Directors

18 December 2013

Dear Colleague,

The surgical management of urinary incontinence and pelvic organ prolapse

We are writing to all practitioners involved in the surgical management of urinary incontinence (UI) or pelvic organ prolapse (POP), particularly in regard to the use of surgical mesh. This includes sub-urethral tapes inserted retro-pubically or via the trans-obturator route. For POP, this includes all mesh inserted vaginally or abdominally.

The investigation and management of all such patients should follow National Institute for Health and Clinical Excellence (NICE) guidance (<http://guidance.nice.org.uk/CG171>; <http://www.nice.org.uk/guidance/ipg267>; <http://www.nice.org.uk/guidance/ipg283>). Similarly, where the insertion of mesh is considered, this should also comply with NICE guidance and, for POP, this should be the subject of audit at an appropriate time interval. Ideally, such decisions should be the subject of a multidisciplinary process and local or trust governance procedures.

Of particular relevance in this area are the following important issues:

1. **Consent:** Consent guidance, consent forms and patient information are available from the specialist societies: the British Society of Urogynaecology (BSUG) and the British Association of Urological Surgeons (BAUS) (www.bsug.org.uk and www.baus.org.uk respectively). We strongly recommend standardisation of all consenting processes such that they comply with up to date evidence and risks at a UK level, but more importantly, at an individual or Trust level. Recent concern has arisen because of inappropriate and/or inadequate consenting without specific mention of relevant risks of any particular procedure at an individual or Trust level.
2. **Audit:** NICE recommends that POP mesh insertion should be part of regular audit. We strongly recommend that **all** POP procedures and **all** incontinence operations, but particularly those involving mesh are recorded on a recognised database e.g. the BSUG or BAUS surgical databases (<http://www.bsug.net> and <http://www.baus.org.uk/Sections/female/research-and-audit>).

3. **Adverse event reporting:** Mesh inserted for POP or UI is considered a **medical device** and, to that end, adverse events must be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) (<http://www.mhra.gov.uk>). Guidance on the type of adverse events to report, associated with these devices is available on the MHRA Healthcare Professionals webpages for Urology and Obstetrics, and Gynaecology. Guidance on what to report is also available on the BSUG and BAUS websites.
4. **Surgery for removal of mesh:** Surgery for removal of tapes or prolapse mesh, or repeat surgery for incontinence or prolapse must be performed in units which can demonstrate relevant specialist care (audited by volume and outcome of surgery) and which are recognised by commissioners or via specialised commissioning processes in England.

These are all important considerations when providing quality care, maximising opportunities to involve patients in decision making by fully informing them of the procedures and respective risks.

Yours faithfully,

A handwritten signature in black ink, appearing to read 'Bruce Keogh', with a long horizontal line extending from the end of the signature.

Professor Sir Bruce Keogh
Medical Director, NHS England

Co-authored and supported by:

Dr Catherine Calderwood
National Clinical Director, Maternity and Women's Health, NHS England

Dr David Richmond
President, Royal College of Obstetricians and Gynaecologists

Mr Ash Monga
Chairman, British Society of Urogynaecology

Mr Adrien Joyce
President, British Association of Urological Surgeons

Mr Roland Morley
Chairman, British Association of Urological Surgeons Section of Female,
Neurological and Urodynamic Urology

Executive Summary

Background

The Medicines and Healthcare Products Regulatory Agency (MHRA) has noted recently that concerns about the safety of vaginal tapes/slings and meshes are being expressed by patients' groups. In response to these concerns MHRA commissioned an overview of research on the safety/adverse events of vaginal tapes/slings/meshes for stress urinary incontinence and pelvic organ prolapse. This overview is a review of reviews. It has been undertaken using a *systematic review* approach to explicitly identify, select, assess and summarise recent published systematic reviews. The intention is to provide transparent, evidence-based information for the use of patient groups and policy makers.

Methods

This review presents data on the adverse effects and safety of vaginal slings/tapes for female stress urinary incontinence inserted surgically via retropubic operations, fascial slings and midurethral synthetic slings, and for pelvic organ prolapse.

Seventeen recent systematic reviews were identified. The majority of the reviews were well conducted and reliable. Fourteen reviews reported on stress urinary incontinence (SUI) or urinary incontinence, and three evaluated pelvic organ prolapse. Most of the systematic reviews assessed data from randomised controlled trials (RCTs) which are usually considered the most methodologically rigorous type of study. However, the quality of the RCTs assessed within the systematic reviews, proved to be variable.

Systematic reviews often pool data from two or more studies. This review presents the range of pooled findings from individual systematic reviews for specific adverse events including pain, sexual difficulties, and vaginal erosion. Pooled values were calculated where data were available or as provided by the systematic review authors.

Results

Pain/discomfort after an operation

0% to 22% of women with SUI experienced pain/discomfort after surgery (RCT data from seven SRs). In some of the SRs, the type of pain was specified: the percentage of women who experienced suprapubic pain ranged from 0% to 18%; groin pain ranged 0% to 22%; and persistent pelvic pain was reported in 6% (one SR).

1% to 25% of women who had an operation for pelvic organ prolapse reported pain after surgery (RCT data from two SRs). We note, however, that this higher percentage was obtained from one RCT rather than *pooled* data. Persistent postoperative pain ranged from 2% to 25% (three SRs). The percentage of women with vaginal pain was 2%, perineal pain was 9%, and buttock pain ranged from 3% to 10%.

Sexual difficulties

The most commonly evaluated sexual adverse event was dyspareunia (painful sexual intercourse) which was experienced by 3% to 10% (two SRs) of women with SUI. A third SR reported that 0% of women had dyspareunia. One SR of 16 studies reported that there was no change in sexual function in 56.7% of women, an improvement in 33.9% of women, and a

deterioration in 9.4% of women after a midurethral synthetic sling operation (Jha *et al.* 2012 (1)). Another SR (eight studies) found that 4% to 20% of women reported worsened sexual function after TVT surgery, and the others were unchanged or improved (Serati *et al.* 2009 (2)). This SR (two studies) also reported that sexual function was improved in 19% to 90% women who had transobturator sling surgery.

6% to 57% of women reported dyspareunia following an operation for pelvic organ prolapse (one RCT). New sexual symptoms were observed in 9% to 15% of women across two studies in one SR. One SR (Maher *et al.* 2010 (3)) reported mean post-operative sexual function scores (PISQ-12) that ranged from 12.5 to 37.3 for different types of surgery.

Vaginal erosion

0% to 5% if women with SUI experienced vaginal erosion after a surgical procedure (RCT data from three SRs).

Mesh/tape erosion

0.6% to 7% of women with SUI experienced mesh/tape erosion after surgery (three SRs). We note, however, that the higher percentage was obtained from one RCT rather than *pooled* data. 0% to 10% of women who had an operation for pelvic organ prolapse experienced mesh erosion (RCT data from two SRs). One SR (Feiner *et al.* 2010 (4)) reported weighted averages for mesh erosion that ranged from 4.6% to 10.7% depending on the type of surgery.

Bladder perforation

0% to 9% of women with SUI experienced bladder perforation after surgery (RCT data from seven SRs). Some of the SRs also reported results for bladder perforation and vaginal perforation, or bladder and urethral perforation: 1% to 7% and 0% to 2% (respectively).

0% to 8% of women reported organ damage (one SR with 15 studies of all types) following surgery for pelvic organ prolapse (Jia *et al.* 2010 (5)).

Urinary tract infection

0.2% to 76% of women with SUI experienced urinary tract infection after surgery (RCT data from five SRs). We note, however, that the higher percentage was obtained from one RCT rather than *pooled* data. None of the SRs that evaluated surgical procedures for pelvic organ prolapse reported on urinary tract infection.

Prolapse

0.5% to 16% of women experienced new or recurrent prolapse after surgery for SUI (RCT data from two SRs). Recurrent prolapse occurred in 0% - 15.3% of women after surgery for pelvic organ prolapse.

Haematoma

0% to 4% of women experienced haematoma after surgery for SUI (RCT data from five SRs) and 1% to 3% of women after an operation for pelvic organ prolapse.

Patient (subjective) reported cure rate

45% to 92% of women reported subjective cure (no incontinence). The short-term objective success rate ranged from 87% to 95% (1 SR) for mesh kits commonly used in the treatment of apical vaginal prolapse (Feiner *et al.* 2008).

Quality of life data

Quality of life data was assessed in 12 SRs. However, the data were not always reported, or could not be easily summarised.

Conclusions of the systematic reviews

The SRs report on the effectiveness of one surgical treatment over another in terms of impact on SUI or prolapse and adverse effects. The SR authors suggest that more long-term trials should be conducted to understand more fully the effectiveness and side effects of the different treatment options.

Discussion

In the last ten years, at least 17 systematic reviews have evaluated the safety of vaginal slings/tapes/meshes.

SR findings may vary for a number of reasons including the specification of different inclusion and exclusion criteria such as whether included papers could be for women with SUI and mixed incontinence or for SUI alone.

This review has focused on RCT data where possible, although it appears that the quality of these RCTs was variable based on the SR authors' assessments. In some of the SRs, data were gleaned from single trials, and pooling was not possible. Due to these limitations the findings were not pooled across SRs and the findings should be considered as indicative only and not used to statistically compare one procedure with another.

Overall, the quality of the SRs was good, providing confidence that the majority of relevant studies will have been included.

It is difficult to draw specific conclusions regarding the actual adverse event rates and subjective cure rates from the available literature for specific procedures. What the available evidence does suggest is the following:

- The majority of patients appear to find treatment beneficial in relieving their incontinence, although a significant minority do not report subjectively that treatment has cured their incontinence.
- Rates of adverse events reported appear to be similar regardless of whether women are treated for SUI or pelvic organ prolapse. The exception would appear to be painful sexual intercourse which seems to be more prevalent with treatment for pelvic organ prolapse.
- Evidence on adverse events suggests that whilst on the whole adverse events occur in only a minority of patients, the likelihood of such an event for an individual patient is not insignificant. However, the evidence is somewhat inconclusive as the

ranges of rates of adverse events reported almost all include 0%. This suggests that some groups of patients may be more susceptible than others in developing adverse events or that surgical expertise and experience and patient after care – which may have differed across specific trials included in a review – may play a key role in developing adverse events.

Please add @rcogmail.org.uk in your safe senders list

***The surgical management of urinary incontinence
and pelvic organ prolapse***



Royal College of
Obstetricians &
Gynaecologists

Your RCOG Registration Number: [REDACTED]

18 June 2014

Many of you will have seen or be aware of the request yesterday by the Scottish Health Secretary, Alex Neil MSP, to suspend the use of all mesh for the treatment of urinary incontinence (UI) and pelvic organ prolapse (POP) in Scotland until there is further evidence available regarding its use.

The notice to the Scottish CMO can be found on the Scottish Government website [here](#).

Consequently, I am writing to all Members and Fellows of the RCOG involved in the surgical management of urinary incontinence and/or pelvic organ prolapse, particularly in regard to the use of surgical mesh to alert them to this decision. For POP, this appears to include all transvaginal mesh insertion.

The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing has changed since a letter was sent out to all practitioners before Christmas from Bruce Keogh, co-signed by myself. This was also mentioned in the RCOG member [e-newsletter](#) in December 2013.

This decision will undoubtedly create problems for patients already consented and awaiting such surgery, but will also have ramifications for surgeons reverting to other surgical alternatives which in themselves have risks and complications. Further, this blanket decision fails to distinguish the surgeries involved and groups all tapes for incontinence with mesh for prolapse repair as one. Finally, it also fails to acknowledge the countless numbers of patients who have benefitted considerably from these interventions over the last 15-20 years especially from tapes for stress UI.

I am therefore reiterating below the key issues from last December's joint NHSE/RCOG/BSUG/BAUS letter for your information and I would like to draw to your attention the need for multidisciplinary involvement (as recommended by NICE in its recent urinary incontinence guideline [update](#)) if considering surgery for stress UI or mesh for pelvic organ prolapse repair.

- The **investigation and management** of all such patients should follow National Institute for Health and Care Excellence (NICE) guidance (<http://guidance.nice.org.uk/CG171> ; <http://www.nice.org.uk/guidance/ipg267> ; <http://www.nice.org.uk/guidance/ipg283>). Similarly, where the insertion of mesh is considered, this should also comply with NICE

guidance and, for POP, this should be the **subject of audit** at an appropriate time interval. Ideally, such decisions should be the **subject of a multidisciplinary process** and local or trust governance procedures.

Of particular relevance are the following important issues:

- **Consent:** Consent guidance, consent forms and patient information are available from the specialist societies: the British Society of Urogynaecology ([BSUG](#)) and British Association of Urological Surgeons ([BAUS](#)) and should be given to all patients well in advance of the surgery. We strongly recommend standardisation of all consenting processes such that they comply with up-to-date evidence and risks at a UK level, but more importantly, at an individual or Trust level. Recent concern has arisen because of inappropriate and/or inadequate consenting without specific mention of relevant risks of any particular procedure at an individual or Trust level.
- **Audit:** NICE recommends that POP mesh insertion should be part of regular audit. We strongly recommend that **all** POP procedures and **all** incontinence operations, but particularly those involving mesh are recorded on a recognised database e.g. the BSUG <http://www.bsug.net> or BAUS <http://www.baus.org.uk/Sections/female/research-and-audit> surgical databases.
- **Adverse event reporting:** Mesh inserted for POP or UI is considered a **medical device** and, to that end, adverse events must be reported to the Medicines and Healthcare Products Regulatory Agency ([MHRA](#)). Guidance on the type of adverse events to report, associated with these devices is available on the MHRA Healthcare Professionals webpages for Urology and Obstetrics and Gynaecology. Guidance on what to report is also available on the BSUG and BAUS websites.
- **Surgery for removal of mesh:** Surgery for removal of tapes or prolapse mesh, or repeat surgery for incontinence or prolapse must be performed in units which can demonstrate relevant specialist care (audited by volume and outcome of surgery) and which are recognised by commissioners or via specialised commissioning processes in England.

These are all important considerations when providing quality care, maximising opportunities to involve patients in decision making by fully informing them of the procedures and respective risks.

Yours faithfully,

Dr David Richmond, President, Royal College of Obstetricians and Gynaecologists (**RCOG**)

Mr Ash Monga, Chair, British Society of Urogynaecology (**BSUG**)

Prof Linda Cardozo, President, European Urogynaecological Association (**EUGA**)

Prof Bob Freeman, Vice President, International Urogynaecological Association (**IUGA**)

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Dear [REDACTED]

Many of you will have seen or be aware of the request earlier this week by the Scottish Health Secretary, Alex Neil MSP, to suspend the use of all mesh for the treatment of urinary incontinence (UI) and pelvic organ prolapse (POP) in Scotland until there is further evidence available regarding its use.

[The notice to the Scottish CMO can be found on the Scottish Government website](#)

Consequently we are writing to all Members of BAUS in order to alert those involved in the surgical management of urinary incontinence and/or pelvic organ prolapse, particularly in regard to the use of surgical mesh, to this decision. For POP, this appears to include all transvaginal mesh insertion.

The decision is unexpected and will cause alarm to women not only in Scotland but in the rest of the UK. As far as we are aware, there is no new evidence to support this suspension and nothing has changed since a letter was sent out to all practitioners in December 2013 from Sir Bruce Keogh.

This decision will undoubtedly create problems for patients already consented and awaiting such surgery, but will also have ramifications for surgeons reverting to other surgical alternatives which in themselves have inherent risks and complications. Further, this blanket decision fails to distinguish the different surgeries involved and groups all tapes for incontinence with mesh for prolapse repair as one. Finally, it also fails to acknowledge the countless numbers of patients who have benefitted considerably from these interventions over the last 15-20 years particularly from tapes for stress UI.

We are therefore reiterating below the key messages from last December's letter from Sir Bruce which was co-authored by the RCOG, BSUG and BAUS. We would like to draw to your attention the need for multidisciplinary involvement, as recommended by [NICE in its recent urinary incontinence guideline update](#), if considering surgery for stress UI or mesh for pelvic organ prolapse repair.

"The investigation and management of all such patients should follow [NICE guidance](#). Similarly where the insertion of mesh is considered this should also comply with NICE guidance and for POP this should be the subject of audit at an appropriate time interval.

Ideally, such decisions should be the subject of a multidisciplinary process and local or trust governance procedures.

Of particular relevance in this area are the following important issues:

1. Consent. Consent guidance and consent forms and patient information are available from the specialist societies: the British Society of Urogynaecology (BSUG) and the British Association of Urological Surgeons (BAUS) (www.bsug.org.uk and www.baus.org.uk respectively). We strongly recommend standardisation of all consenting processes such that they comply with up to date evidence and risks at a UK level, but more importantly, at an individual or Trust level. Recent concern has arisen because of inappropriate and or inadequate consenting without specific mention of relevant risks of any particular procedure at an individual or Trust level.
2. Audit. NICE recommends that POP mesh insertion should be part of regular audit. We strongly recommend that all POP procedures and all incontinence operations, but particularly those involving synthetic mesh are recorded on a recognized database e.g. the BSUG or BAUS surgical databases (<http://www.bsug.net> and <http://www.baus.org.uk/Sections/female/research-and-audit>).
3. Adverse event reporting. Mesh inserted for POP or UI is considered a medical device and to that end adverse events must be reported to Medicines and Healthcare Products Regulatory Agency (MHRA) (<http://www.mhra.gov.uk>). Guidance on the type of adverse events to report associated with these devices is available on the MHRA Healthcare Professionals webpages for Urology and Obstetrics and Gynaecology. Guidance on what to report is also available on the BSUG and [BAUS websites](#).
4. Surgery for removal of mesh. Surgery for removal of tapes or prolapse mesh or repeat surgery for incontinence or prolapse must be performed in units which can demonstrate relevant specialist care (audited by volume and outcome of surgery) and which are recognized by Commissioners or via Specialised Commissioning processes in England.

These are all important considerations when providing quality care, maximizing opportunities to involve patients in decision making by fully informing them of the procedure and respective risks.”

[Further links to MHRA and BAUS guidance and the York report.](#)

Some of you will be aware, NHS England is leading work to address concerns from both the clinical and patient community regarding surgical procedures for Pelvic Organ Prolapse and Stress Urinary Incontinence using vaginal mesh.

NHS England is setting up a working group to establish the reasons for these concerns and identify potential ways to address them. This group will consist of representatives from NHS England, the Department of Health, the Scottish Government and the Medicines and Healthcare Products Regulatory Agency. Also represented will be the specialist societies BSUG and BAUS), and the Royal College of Obstetricians and Gynaecologists. Patient

representatives will be invited, including those from the group Meshes United. The Wales and Northern Ireland Governments will be kept informed as the work progresses.

The group will be chaired by Professor Keith Willett, National Director for Acute Episodes of Care, NHS England and the first meeting of the working group will be on 16 July 2014. We will keep you informed of progress.

Yours sincerely

Adrian Joyce

Mark Speakman

Roland Morley



SCOTTISH PELVIC FLOOR NETWORK (SPFN) STATEMENT

THE USE OF SYNTHETIC MID-URETHRAL SLINGS FOR THE TREATMENT OF STRESS URINARY INCONTINENCE IN WOMEN

June 2014

“In line with the National Institute of Clinical Excellence Guideline CG171, the Management of Urinary Incontinence in Women, the SPFN supports the use of Synthetic Mid-Urethral Slings in surgical treatment of stress urinary incontinence in women wishing to proceed for surgical treatment after failure of the conservative treatment options. The SPFN also supports the current credible medical research in this field.”

Dear SPFN Member,

This statement is issued in response to the recent media attention regarding the use of transvaginal mesh (TVM) for treatment of pelvic organ prolapse (POP) in women; this has later extended to include the use of synthetic mid-urethral slings (SMUS) for treatment of stress urinary incontinence (SUI). The Scottish Health Minister has recently announced, without discussion with health professionals, the decision to suspend the use of TVM and SMUS throughout NHS Scotland.

The above has led to increasing concerns to women awaiting surgical treatment for SUI and POP. There are also concerns at senior management level in some health boards about potential increase in litigations. Legal liability for individual health boards has been largely related to the adequacy of pre-operative counselling and provision of information to patients.

The SPFN emphasizes that patients should be provided with the appropriate information and counselling regarding procedure-related risks, outcomes, and alternative treatment options. This will enable patients to make an informed choice regarding their treatment and fully consider the implications of different surgical and non-surgical options available. The SPFN stresses that the information given to patients should be based on the best available medical evidence, rather than anxieties arising from media attention and/or from litigations.

The SPFN has been working with the Scottish Government and representatives of the mesh-injured women within a Short-Life Working Group (SLWG) that started in 2013; a comprehensive patient information leaflet on SMUS has recently been produced. Pathways for management of POP and management of TVM complications will be available from the SLWG later this year. The SPFN recommends to its members the use and implementation of these documents.

In providing evidence for best practice, it is most important to recognize the fundamental differences between (a) SMUS used for treatment of SUI and (b) TVM used in POP surgery. Although they are both made of the same synthetic material (Type 1 polypropylene mesh), they vary significantly regarding the volume of mesh used, the mode of insertion and the availability of supporting evidence for their safety and effectiveness. An overwhelming wealth of medical evidence supports the use of SMUS as a first line surgical treatment for SUI in women wishing to proceed to surgery after failure of conservative management. The current robust medical evidence¹⁻³ shows that SMUS are both safe and effective minimal invasive procedures with similar efficacy and significantly less rates of peri-operative morbidity and earlier recovery, compared to the alternative surgical procedures such as Burch Colposuspension (open and laparoscopic) and

autologous slings. The FDA⁴ has recently proposed to reclassify TVM for treatment of POP to level III i.e. high-risk procedures. FDA clarified that the reclassification does not apply to SMUS for SUI or mesh for other indications, such as abdominal sacrocolpopexy and hernia.

In line with the National Institute of Clinical Excellence (NICE) Guideline CG171 “The Management of Urinary Incontinence (UI) in Women”³, the SPFN supports the use of SMUS for surgical treatment in women with SUI. Implementation of the NICE guideline has been specifically supported in a letter by the Medical Director NHS England in December 2013; supported and co-signed by the President of the Royal College of Obstetricians & Gynaecologists (RCOG), the chairmen of the British Society of Urogynaecology (BSUG) and the British Association of Urological Surgeons (BAUS). Similarly, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)⁵ and the American Urogynaecological Society (AUGS) jointly with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU)⁶ have issued position statements in March 2014, supporting the use of SMUS in treatment of SUI in women based on the best available evidence. Most recently, the International Urogynaecology Association (IUGA) has also drafted a similar statement.⁷

The SPFN proposes that MHRA reporting of complications should be made mandatory. The SPFN also encourages its members to regularly audit the results of the surgical procedures performed for SUI and POP, preferably using a national registry (BSUG/BAUS), and to discuss the audit results during their annual appraisal. The Health Boards in Scotland are urged to facilitate the introduction of national registries to routine practice.

The SPFN continues to lead the way in creating the best available evidence for surgical and conservative treatment options for SUI and POP in women, through high quality nationally funded and ethically approved research projects. The SPFN currently leads 2 large multicentre HTA-funded clinical trials in the field of UI in women: (a) The “SIMS Study” investigating the best type of SMUS to be performed in women with SUI. The SIMS trial aims to assess if a “mini-sling” with 50% less mesh volume, robust anchoring mechanism and performed with less invasive surgery can lead to improved outcomes in women undergoing surgery for SUI; (b) The “OPAL Study” investigating the optimal regime for pelvic floor exercises and biofeedback for non-surgical treatment of SUI in women. Patient-reported outcomes, complications, and effect on patients’ urinary symptoms and quality of life are the main end points of both studies emphasizing that patients’ experience and satisfaction are at the centre of SPFN-led medical research. Many units in the UK are recruiting centres for both trials; the SPFN recommends that eligible patients are offered to participate and welcomes the Health Minister’s decision to exempt approved medical research (SIMS Study) from the decision of mesh suspension.

The SPFN will continue to (a) support healthcare professionals in managing their patients with SUI and POP according to the best available clinical evidence, and (b) empower patients with high quality medical information that would enable them to make an informed decision regarding their treatment options.

Kind Regards
SPFN Steering Committee

References:

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6. <http://www.augs.org/guidelines-statements>
7. <http://www.iuga.org/?page=slings>

Manufacturer	Product brand	Indication	The manufacturer and reviewer conclusions on risk assessment	Extracts from audit reports that contribute to the risk assessment	PMS activities data
<p>Manufacturer A</p>	<p>Product A</p>	<p>POP</p>	<p>A risk/hazard acceptability memo (November 2, 2009) summaries all the risk analysis (dFMEA, pFMEA) and concludes that all hazards have been evaluated and the overall risk of [REDACTED] s acceptable (approved by corporate medical director).</p> <p>Minor NC raised by reviewer – not meeting requirements of ISO 14971:2012.</p>	<p>All key risk have been identified (60 risks identified): erosion, infection, insufficient vaginal support, mesh breaks during placement, insufficient suture, dyspareunia. All risks have control measures. The risk score based on severity, occurrence and detection. For severity scores of 9 and 10 had to be mitigated regardless of risk score (new procedure, [REDACTED]). All risks are within the acceptable level. The PMS procedure [REDACTED] confirms that the risk analysis is to be updated if new risks are identified.</p>	<p>The clinical evaluation report (update) summaries the market experience, in the review period (March 2011 – February 2013) [REDACTED] were sold. The following complaints are recorded – break 2 (0.02%), component missing 1 (0.01%), no known device problem 8 (0.07%).</p> <p>There is no PMCF, device was launched in August 2009. The PMS plan is collected every two years.</p>
<p>Manufacturer A</p>	<p>Product B</p>	<p>UI</p>	<p>Key risks selected for review found to be satisfactory.</p> <p>Minor NC raised by reviewer – not meeting requirements of ISO 14971:2012.</p>	<p>The most recent risk analysis was conducted in July 2012, ref. [REDACTED] Rev. 13. 211 specific risks are identified.</p>	<p>A clinical investigation has been conducted since launch, final report date 20th June 2011. The investigation enrolled 52 patients in a multi-centre study for evaluation after treatment for urinary stress incontinence with the primary end-point being a reduction in incontinence (a) during strenuous activity, (b) during normal activity, and (c) in the supine position.</p> <p>Overall, in the clinical investigation, 86.3% of patients successfully resulted in improvement or restoration of continence.</p> <p>Secondary end-points relating to quality of life showed 100% patients reporting improvement.</p>

					<p>The most recent PMS report is dated 19th February, 2013 and reviews the period Nov 2010 to Oct 2012.</p> <p>The PMS report details the complaints summary of all [REDACTED] product codes: In total complaints rate is 1.165% of total sales (i.e. 228 complaints of 19569 sales). Highest complaints are: Anchor breaks, 32.2% No known device problem, 14.7% Other breaks, 13.1% Device inoperable, 9.4% Bent, 4.9% Approximately 15 other categories listed, range 3.5% - 0.4%</p>
Manufacturer A	Product C	POP	<p>The manufacturer has concluded that the risk benefit ration remains favourable to the devices.</p> <p>Reviewed and accepted.</p>	<p>Risk management has been updated to include information on emerging risks and hazards based on Complaints, PMS data, and vigilance reports. The new risks and hazards have been assessed and the current controls were deemed adequate to mitigate them. It was noted that there is a rise in complaints, especially in the US, related to litigation associated with the mesh devices. Even taking this into account the manufacturer has concluded that the risk benefit ration remains favourable to the devices.</p>	<p>A summary of complaints was provided from June 2007-2011. In this period, sales for the [REDACTED] were [REDACTED] units worldwide and [REDACTED] units in the EU. The complaint rate for [REDACTED] worldwide is 1.21% and EU is 0.26%.</p> <p>The manufacturer has noted that the recent rise in complaint rates is related to complaints associated with litigation in the USA. [REDACTED] complaints in 2012 and [REDACTED] complaints in 2011 were stated as related to litigation for devices remaining within the patients.</p> <p>The manufacturer also stated that the total number of complaints (combined for [REDACTED]) that were not of legal origin remain at around 0.1%. The complaint rate in the EU is considered low and acceptable. The complaint rate in the US has gone up due to litigations and market conditions. It is not entirely clear if the litigation associated complaints are device-</p>

					<p>related or due to poor patient selection and surgical procedures.</p> <p>■ vigilance incidents have been reported in the EU for the ■ devices. These reports were filed for tearing of the device at the level of the arms, ■ cases of infection and erosion within weeks of implantation, ■ of removal after erosion, and ■ for erosion of mesh with pain, bleeding and discomfort since procedure.</p> <p>The manufacturer also noted that they have stopped selling the ■ devices in the US considering the current market conditions – litigations, FDA requirements for Post Market trials, and changing physician preferences to single incision devices. However, the number of complaints continues to remain low (0.26%) in the EU and hence the manufacturer intends to continue placing these devices on the EU market.</p> <p>This review was conducted in January 213 at renewal, and as part of the renewal a request was made to the Manufacture to provide periodic summary reports at least annually to establish continued safety and performance of the device in the EU.</p> <p>In January 2014 a summary report was submitted to ■ for ■ The time frame for the summary was November 2012 to October 2013. ■ units were sold into Canada, Europe and LAPAC. No complaints were received from these geographies. ■ discontinued selling these products in the US in June 2012. However during the review period, ■ complaints were received in the US for the devices that</p>
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					were previously implanted. █ of these related to device remains implanted. The majority of these are due to litigation, investigation by █ determined that these complaints are not related to a specific device failure. █ concluded that continued evaluation of the risks associated with the device and the literature support the benefits outweigh any risks.
Manufacturer B	<p>█</p> <p>Extracts from surveillance Technical audit dated 10 June 2013</p> <p>█</p> <p>Product A</p>	POP	<p>Manufacturer conclusion: Confirms RMP satisfactorily fulfilled, overall residual risk acceptable and appropriate methods in place to obtain production & post-production information</p> <p>█</p> <p>Conclusion: Generally acceptable with gaps identified which were raised as NCRs. Corrective action plan provided. Due for followup in 2015.</p>	<p>█ Risk Management File consists of-</p> <ul style="list-style-type: none"> • RMR – █ Rev. G, dated N/R o Identifies name and revision of documents reviewed to support RMR (including RMP, PMSR, CES, Human Factors, dFMECA, pFMEA, product quality data review, CEA) o Confirms RMP satisfactorily fulfilled, overall residual risk acceptable and appropriate methods in place to obtain production & post-production information § Controls in place for all risks § No risks were mitigated solely by labeling o Demonstration of compliance to EN ISO 14971:2012 was not evident - Does not include risk/benefit analysis; procedure does not require this to be done as all risks were identified as being acceptable 	<p>Extract from Clinical Section</p> <p>References 3 clinical trials</p> <ul style="list-style-type: none"> o █ Retrospective Chart Review (Trial # █ § Multicenter, retrospective review @ 15 sites in US btwn 21 May – 3 Jun 2005, n=208 w/ f/u> 6wks o █ (Trial █) – █ § Observational collection of short- and long-term patient outcomes – post-marked, longitudinal, 20 center study w/ 2-year f/u, n=623 o █ – Phase I, III, and IV § Prospective, multi-phase, 28 center study to evaluate long-term safety & efficacy, n=167 <ul style="list-style-type: none"> • Clinical trial conclusions – no life-threatening conditions, unanticipated adverse device effects or events that resulted in non-reversible serious impairment of body structure or function. Supports device is safe and effective for intended use w/in 2 year post surgery period. • Literature review – no literature citations for equivalent devices (internal to █ external) <ul style="list-style-type: none"> o Objective defined o Search database, terms, inclusion / exclusion

				<ul style="list-style-type: none"> - Does not identify whether all risks have been reduced as far as possible □ procedure does not require this to be done ██████████ raised against the gap. • dFMECA – ██████████ ██████████ <p>Extrusion probability – projected rate is sum of all individual rates à 2.3% à similar ballpark as literature / clinical trials (especially if considered in conjunction w/ erosion)</p> <ul style="list-style-type: none"> o Reasons for extrusion: <ul style="list-style-type: none"> § Shape & size of mesh § poor tissue ingrowth § material, fiber dia, kit density, heat process § unable to withstand mechanical req post-impl § tissue ingrowth causes mesh to shrink in length § material and pore size § design or rivet material & geometry § IFU confusing, no instructions § Physician misuse or failure to follow recommended directions for use § Insufficient patient counseling 	<p>criteria defined</p> <ul style="list-style-type: none"> o Review covered 1 Jan 2009 – 13 Oct 2011 o Identified 69 articles and abstracts o Analyzed 5 manuscripts and 13 conference abstracts, n=897, f/u up to 24 months o Summarized individual articles (Biblio ref, sample size, study design identifying device used, f/u period, objective success definition, subjective success definition, success rates, intra-op complications, peri-/post-op complications, author conclusions) o Included analysis of articles and representation to EU patients § Summarized key risks seen in literature but did not really address benefits or alternative treatments / analysis of state-of-the-art § No risk/benefit analysis. o Complications ref: <ul style="list-style-type: none"> § Rectal injury, perineal hematoma, buttock pain, dyspareunia, extrusion, infection, fever, UTI, urinary retention, de novo bladder urgency, bladder injury, de novo detrusor instability, pudendal neuropathy, hemorrhage, erosion, persistent discomfort, healing abnormalities, anterior prolapse, stress incontinence, cystoceles, granuloma formation, dehiscence o Concluded: Supports device is safe and effective for intended use w/in 2 year post surgery period. Results consistent w/ safety results obtained in ██████████ studies • PMS – references PMS Report, ██████████
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			<ul style="list-style-type: none"> • dFMECA – [REDACTED] rev. E <p>o Highest risks (risks that require justification as per risk SOP):</p> <ul style="list-style-type: none"> § Too much tension on the graft due to shape & size of graft causing erosion or extrusion § Mesh graft does not promote tissue in-growth due to material / fiber dia / knit density causing erosion or extrusion § Mesh arm does not promote tissue in-growth due to material / fiber dia / knit density causing erosion or extrusion § Separation of mesh arm rivet connection during procedure due to rivet matl causing prolonged procedure <p>o Justification compared to complaint rate and CES and referenced PMSR. Drew conclusion that rates are acceptable without explanation. [REDACTED]</p> <p>pFMEA – [REDACTED] [REDACTED]</p> <p>Acceptability:</p>	<ul style="list-style-type: none"> o Covers period from 1 May 2009 – 30 Apr 2011 o Objective to ensure risk estimation is still acceptable and consistent w/ RMF and to identify any risks not previously recognized o Did not identify any new risks. o Stated all complaint rates consistent w projected rates. o Risks and safety profiles aligned w/ clinical literature findings and consistent w/ current RMF. o Reviewed by RA, R&D, CA, QE; Report also signed by Clin & Reg Mgrs. o PMS AE Justification: States differences in rates seen in complaints, risk, CES and states that they are acceptable but does not discuss this at all. Literature / clinical trials have highest AE rates and some > 10%. It is not clear why these are considered acceptable and why RMF does not reflect highest risk levels. [REDACTED] o PMS Activities Reviewed: § Complaints – Complaint of incontinence identified in IFU as a risk but was not in RMF. Resulted in action to add to RMF. ∅ [REDACTED] old w/in review period; [REDACTED] complaints – Highest complaints: pain (0.49%), wrinkling/folding (0.25%), incontinence (0.22%), dyspareunia (0.22%), erosion (0.20%), voiding dysfunction (0.18%), Extrusion (0.17%), UTI (0.12%), Mental pain (0.12%), infection (0.11%), prolapse recurrence (0.05%) ∅ Only sold outside of US after 31 Mar 2013 – [REDACTED] business decision to not sell in US due to need for additional RCTs (522 studies) by FDA
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				<p>§ An RPN of 70 or less is considered acceptable. Risks that remain unacceptable after the implementation of risk control measures will be evaluated through a risk vs. benefit analysis. If the benefit outweighs the risk, then justification can be used to accept the risk.</p> <p>o Highest risks (risks that require justification):</p> <p>§ RPN = 57: Sheath causes mesh to be twisted or distorted due to operator error resulting in erosion à No control, no detection (not consistent with EN ISO 14971:2012)</p> <p>██████</p>	<p><input type="checkbox"/> Highest Projected Rates of Clinically Relevant Complaints (sum of individual opportunities for failure):</p> <ul style="list-style-type: none"> - Extrusion: 2.36% - Erosion: 1.99% - Sum of Extrusion & Erosion: 4.35% - Pain: 1.32% - Prolapse Recurrence: 0.92% - Dyspareunia: 0.76% <p><input type="checkbox"/> Clinical study & lit review – No action</p> <p><input type="checkbox"/> Reported complication rates for extrusion – consistent btwn risk & CES – could be clearer</p> <ul style="list-style-type: none"> - Clinical Trials: 13.9%, 1.3%, 7.2%/7.3% - Lit. Review Overall: 4.1% Note: Lit. frequently confuses erosion & extrusion - Lit Rev. Papers: 10%, 12.5%, 25.7%, n/r, 0 - Lit Rev. Abstracts: 4.3%, 6%, 1.7%, 10.6%, 2.8%, 6.5%, 6 abstracts – 0%, 2 abstracts – N/R <p><input type="checkbox"/> FU/OR Manual review – recommended adding 2 statements be considered for inclusion in IFU:</p> <p><input type="checkbox"/> “Safety and effectiveness of synthetic mesh in transvaginal surgical procedures to treat pelvic organ prolapse have not been evaluated in a prospective, randomized clinical study” <input type="checkbox"/> This is present in the current IFU.</p> <p><input type="checkbox"/> “Known risks of surgical procedure include defect healing or wound dehiscence, recurrent prolapse, prolapse occurring in other compartments, dyspareunia, pelvic pain, infection and De Novo/worsening urinary incontinence”. <input type="checkbox"/> This is present in the current IFU.</p>
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				<p><input type="checkbox"/> Product standards – Verify ref. to ISO 14155 have been replaced with MEDDEV 2.7.1 and GHTF N2R8 (since clinical trials no longer active).</p> <p><input type="checkbox"/> Previous PMSR actions reviews – No actions</p> <p><input type="checkbox"/> PMCF Plan – No actions</p> <p>Clinical Evidence Summary Report: [REDACTED] [REDACTED] dated 26 Jan 2012 (Note: this is a subsequent revision to [REDACTED] dated 26 Jan 2010) – by procedure, this is scheduled to be reviewed and updated in Jul 2013</p> <ul style="list-style-type: none">• 2 Authors: RN, MBA contractor and [REDACTED] Clinical Research Specialist (MS, CCRP) – CV included and justifies competency• Prepared according to MEDEV 2.7.1/Rec. 3• Indication in CES do not match IFU/TF/RMF. Lists general intended use where the connective tissue has ruptured or for implantation to reinforce soft tissues where weakness exists in the urological, gynecological, and gastroenterological anatomy. This includes but is not limited to the following procedures: pubourethral support, including urethral slings, vaginal wall prolapse repairs including anterior and posterior wall repairs, vaginal suspension, reconstruction of the pelvic floor and tissue repair. [REDACTED]• References 4 clinical trials <p>o [REDACTED] Chart Review (Trial # [REDACTED])</p> <p>§ Same as above</p>
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				<ul style="list-style-type: none"> o [REDACTED] Registry (Trial # [REDACTED]) § Observational collection of short- and long-term patient outcomes – post-marked, longitudinal, 20 center study w/ 2-year f/u, n=918 o [REDACTED] – Phase I, III, and IV § Prospective, multi-phase, 28 center study to evaluate long-term safety & efficacy, n=81 o [REDACTED] Clinical Trial (Trial # [REDACTED]) § Prospective, multicenter, single-arm study to evaluate long-term outcomes of [REDACTED] to treat ≥ Stage II symptomatic anterior vaginal wall prolapse, n=114 @ 5 sites w/ median f/u = 23.5 mo <ul style="list-style-type: none"> • Clinical trial conclusions – the safety profiles and the efficacy rates are consistent with that found in the literature. No life-threatening conditions, unanticipated adverse device effects or events that resulted in non-reversible serious impairment of body structure or function. Supports device is safe and effective for intended use w/in 2 year post surgery period. • Literature review – no literature citations for equivalent devices (internal to [REDACTED] external) o Objective defined o Search database, terms, inclusion / exclusion criteria defined o Review covered 1 Jan 2009 – 24 Oct 2011 o Identified 133 articles and abstracts o Analyzed 15 manuscripts and 14 conference abstracts, n=2003, f/u up to 52 months o Summarized individual articles (Biblio ref, sample size, study design identifying device used, f/u period, objective success definition, subjective
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					<p>success definition, success rates, intra-op complications, peri-/post-op complications, author conclusions)</p> <ul style="list-style-type: none">o Included analysis of articles and representation to EU patients§ Summarized key risks seen in literature but did not really address benefits or alternative treatments / analysis of state-of-the-art§ No risk/benefit analysis. [REDACTED]o Complications ref:<ul style="list-style-type: none">§ Urinary retention, dyspareunia, vaginal extrusion, fever, UTI, vaginal adhesion, hemorrhage, perineal hematoma, transient leg pain, levator pain, groin discomfort, urgency, stage 2 rectocele, vaginal narrowing, bladder injury, sexual dysfunction, urinary incontinence, voiding difficulty, persistent sensory urgency, persistent motor urgency, mesh folding, transient gluteal pain, febrile episodes, bladder outlet obstruction > 72 hrs, mesh erosion, urinary residuals, reactive enterocele / rectocele, uterus prolapse, mesh contraction, overactive bladder, vaginal bleeding, protrusion, severe blood loss, laeration of the anterior wallo Concluded: Supports device is safe and effective for intended use. Results consistent w/ safety results obtained in [REDACTED] clinical studies.• PMS – references PMS Report, [REDACTED] [REDACTED] dated N/Ro Covers period from 1 Jul 2009 – 30 Jun 2011o Objective to ensure risk estimation is still acceptable and consistent w/ RMF and to identify any risks not previously recognizedo Did not identify any new risks.
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					<p>o Stated all complaint rates consistent w projected rates.</p> <p>o Risks and safety profiles aligned w/ clinical literature findings and consistent w/ current RMF.</p> <p>o Reviewed by RA, R&D, CA, QE; Report also signed by Clin & Reg Mgrs.</p> <p>o PMS AE Justification: States differences in rates seen in complaints, risk, CES and states that they are acceptable but does not discuss this at all. Literature / clinical trials have highest AE rates and some > 10%. It is not clear why these are considered acceptable and why RMF does not reflect highest risk levels. [REDACTED]</p> <p>o PMS Activities Reviewed:</p> <p>§ Complaints – Complaint of incontinence identified in IFU as a risk but was not in RMF. Resulted in action to add to RMF.</p> <p>Ø [REDACTED] sold w/in review period; [REDACTED] complaints – Highest complaints: pain (0.35%), wrinkling/folding (0.24%), Extrusion (0.24%), incontinence (0.21%), prolapse recurrence (0.16%), dyspareunia (0.15%), erosion (0.15%), infection (0.14%), voiding dysfunction (0.13%), UTI (0.11%)</p> <p>Ø Only sold outside of US after 31 Mar 2013 – [REDACTED] business decision to not sell in US due to need for additional RCTs (522 studies) by FDA</p> <p>Ø Highest Projected Rates of Clinically Relevant Complaints (sum of individual opportunities for failure):</p> <ul style="list-style-type: none"> - Extrusion: 4.20% - Erosion: 3.86% - Sum of Extrusion & Erosion: 8.06%
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					<ul style="list-style-type: none"> - Pain: 2.52% - Prolapse Recurrence: 1.38% - Infection / UTI: 0.86% - Voiding dysfunction: 0.80% <p>§ Clinical study & lit review – No action</p> <p>∅ Reported complication rates for extrusion – fairly consistent btwn risk & CES – could be clearer</p> <ul style="list-style-type: none"> - Clinical Trials: 13.9%, 4.1%, 3.7%/5.4% - Lit. Review Overall: 3.15% Note: Lit. frequently confuses erosion & extrusion - Lit Rev. Papers: 6.3%, 12.5%, 5.5%, 5.4%, 4.5%, 7.1%, 8.7%, 5.2%, 4.1%, 2-N/R, 2 – 0, 3 – report erosion (18.2%, 3.7%, 2.9%) <p>§ IFU/OR Manual review – recommended adding 2 statements be considered for inclusion in IFU:</p> <p>∅ “Safety and effectiveness of synthetic mesh in transvaginal surgical procedures to treat pelvic organ prolapse have not been evaluated in a prospective, randomized clinical study” à This is present in the current IFU.</p> <p>∅ “Known risks of surgical procedure include defect healing or wound dehiscence, recurrent prolapse, prolapse occurring in other compartments, dyspareunia, pelvic pain, infection and De Novo/worsening urinary incontinence”. à This is present in the current IFU.</p> <p>§ Product standards – Verify ref. to ISO 14155 have been replaced with MEDDEV 2.7.1 and GHTF N2R8 (since clinical trials no longer active).</p> <p>§ Previous PMSR actions reviews – No actions</p> <p>§ PMCF Plan – No actions</p> <p>Women’s Health Mesh Product Complaint Trend</p>
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					<p>Investigation Summary, [REDACTED] 30 Mar 2012 – Requested but not associated with TF. Note: It is clear it would be captured upon next revision to CES/PMSR but is significant increase in trend during interim.</p> <ul style="list-style-type: none"> • Showed analysis of increased trending of complaints since FDA Warning about Transvaginally placed meshes in July 2011 and subsequent increase in litigation. • Captures data on [REDACTED] in addition to 2 other [REDACTED] devices. • [REDACTED] complaints increased from baseline of approx. 0 - 1% 3-month moving avg rate to > 8% from 2010/2011 to Jan 2012 • Nature of complaints as follows (approx.): pain (20%), other medical condition (17%)m erosion (15%), removal (8%), dyspareunia (7%), extrusion (6%), infection(5%), followed by (fibrosis, incontinence, bleeding, dysuria, UTI, graft exposed, prolapse recurrence – ranging from 4% - 1%). • Recommends that complaints continue to be monitored for trends within problem categories. This should be accomplished through normal business practice of monthly Product Quality Data Reviews and annual PMSRs. • Next PMSR scheduled for July 2013.
<p>[REDACTED] Manufacturer B</p>	<p>[REDACTED]</p>	POP	<p>[REDACTED] claims that the overall residual risk posed by this device is acceptable.</p>	<p>RMF: [REDACTED] dated 8 Feb 2011 (Note: Also includes plan</p>	<p><u>Initial approval in Sep 2011. PMS data yet to be reviewed and will be reviewed as a part of the renewal in 2016 or any substantial change submission related to this device prior to the</u></p>

	Product B		<p>██████████ It is confirmed that the risk analysis evaluates both design and process risks, is linked to Clinical Evaluation / PMS information, and evaluates risk throughout the lifetime of the device.</p> <p>The risk assessment and conclusions drawn are considered satisfactory</p>	<p>for ██████████ which is not part of dossier). Plan includes scope, responsibilities & authorities (R&D, QE, ME, Clinical, RA, Mktg, Microbiology, Pkg Engr, Proj Mgr), criteria for acceptability, verification activities, production & post-production activities</p> <ul style="list-style-type: none"> • dFMECA, ██████████ approved 16 Sept 2011; supplemental approval of Pkg, Micro, Proj. Mgr functions on 27 Sept 2011 • Clinical Effects Analysis (CEA) for ██████████ • pFMEAs <ul style="list-style-type: none"> o ██████████ Rev. B – ██████████ o ██████████ Rev. D – ██████████ o ██████████ Rev. E – Coating the ██████████ o ██████████ Rev. D – ██████████ o ██████████ Rev. E – Arm Assembly, TFE / Mesh / Rod for Elevate o ██████████ Rev. B – Accessory Assembly, Arm / Eyelet Hldr o ██████████ Rev. B – Assemble ██████████ • RMR, # ██████████, Rev. 1 – includes ref. to rest of RMF including 	<p>renewal. A summary of the clinical evaluation reviewed at the time of initial approval is provided below.</p> <p>The ██████████ System belongs to ██████████ family, which contains two generations of devices ██████████</p> <p>The two generations of devices share substantial similarities. Therefore, the clinical evidence established for ██████████ can provide valuable information for the ██████████ which contains two devices: ██████████</p> <p>██████████ Furthermore, The main difference between the ██████████ and the existing ██████████ are that the central mesh of the former is coated by ██████████</p> <p>██████████ As a result, the clinical evidence established for the ██████████ is the most relevant clinical evidence for the ██████████ This is due to the fact that the ██████████ does not change the intended use of the ██████████ nor does it alter its fundamental scientific technology. There are no other ██████████ meshes used as implantable medical device(s) currently available on the market.</p>
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			<p>RMP, dFMEA, CEA, and pFMEAs above; scope, summary of changes, ref. to RMP, risk control summary, completeness of risk evaluation, overall residual risk acceptability, post-production monitoring plans</p> <p>RMF: [REDACTED] ev. 1, dated 8 Feb 2011 (Note: Also includes plan for [REDACTED] which is not part of dossier). Plan includes scope, responsibilities & authorities (R&D, QE, ME, Clinical, RA, Mktg, Microbiology, Pkg Engr, Proj Mgr), criteria for acceptability, verification activities, production & post-production activities</p> <ul style="list-style-type: none"> • dFMECA, [REDACTED] approved 16 Sept 2011; supplemental approval of Pkg, Micro, Proj. Mgr functions on 27 Sept 2011 • Clinical Effects Analysis (CEA) for [REDACTED] Rev. F • pFMEAs <ul style="list-style-type: none"> o [REDACTED] Rev. B – [REDACTED] Solution o [REDACTED] Rev. 1 – Ink Mixing 	<p>Study Outcomes – (comparable)</p> <table border="1"> <thead> <tr> <th>Study # (identified above)</th> <th>Device</th> <th>Pre-op Dia</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>[REDACTED]</td> <td>All patients had : posterior vaginal prolapse and/or (or cervix) descent</td> </tr> <tr> <td>2</td> <td>[REDACTED]</td> <td>All patients had : anterior vaginal apical prolapse</td> </tr> </tbody> </table>			Study # (identified above)	Device	Pre-op Dia	1	[REDACTED]	All patients had : posterior vaginal prolapse and/or (or cervix) descent	2	[REDACTED]	All patients had : anterior vaginal apical prolapse
Study # (identified above)	Device	Pre-op Dia													
1	[REDACTED]	All patients had : posterior vaginal prolapse and/or (or cervix) descent													
2	[REDACTED]	All patients had : anterior vaginal apical prolapse													

				<p>o [redacted] Rev. E – [redacted]</p> <p>o [redacted] Rev. D – Printed Ant</p> <p>o [redacted] Rev. D – [redacted]</p> <p>Highest Risk Levels: [redacted] Note: number references below relate to row in dFMEA.</p> <p>dFMECA: 5 of the 305 identified hazards required justification for approval (in the RMR). These were judged acceptable. The other 300 fell within the acceptable range. 1 identified hazard (#210 – off-label use) was not analyzed as [redacted] has no control over this. This is considered acceptable.</p> <p>251. (Minor x Remote) Unable to load / Anchor not loaded correctly to needle tip (may rotate or separate during placement) due to physician not properly loading mesh arm & sheath resulting in a prolonged procedure.</p> <p>260. (Minor x Remote) Anchor is not inserted adequately to the muscle and doesn't hold due to surgical techniques or physician does not follow recommended directions for use</p>	<table border="1"> <tr> <td data-bbox="1422 193 1619 256"></td> <td data-bbox="1619 193 1883 256"></td> <td data-bbox="1883 193 2069 256"></td> </tr> <tr> <td data-bbox="1422 256 1619 595">3</td> <td data-bbox="1619 256 1883 595">([redacted])</td> <td data-bbox="1883 256 2069 595">All patients had : anterior vaginal apical prolapse</td> </tr> <tr> <td data-bbox="1422 595 1619 794">4</td> <td data-bbox="1619 595 1883 794">[redacted]</td> <td data-bbox="1883 595 2069 794">All patients had : anterior vaginal apical prolapse</td> </tr> </table> <p>General Literature Review of [redacted] – [redacted] o 25 publications (from 1999 – 2010) for [redacted] implantable medical devices were identified covering 8412 patients (including other test & control grps) w/ f/u range of 48 hrs – 2 yr. Devices were either [redacted]</p> <p>o The reported risks or complications are entirely associated with the nature of [redacted] disease, the procedure, or the [redacted] itself, though some causes may still be unclear. No complications were identified that were attributed directly to the [redacted]</p>				3	([redacted])	All patients had : anterior vaginal apical prolapse	4	[redacted]	All patients had : anterior vaginal apical prolapse
3	([redacted])	All patients had : anterior vaginal apical prolapse												
4	[redacted]	All patients had : anterior vaginal apical prolapse												

			<p>resulting in prolonged procedure.</p> <p>268. (Minor x Remote) Sheath cut out is distorted from first anchor deployment and create difficulty loading the sheath on second arm assembly due to physician misuse or failure to follow recommended directions for use to press the trigger to load / unload the sheath resulting in a prolonged procedure.</p> <p>291. (Serious x Remote) Over tension and unable to loosen the mesh once locking eyelets are in place due to surgical techniques or physician does not follow recommended directions for use resulting in vaginal extrusion; voiding dysfunction; pain; urinary / defactory retention / obstruction; prolapsed recurrence; dyspareunia.</p> <p>292. (Minor x Remote) Over tension and unable to loosen the mesh once locking eyelets are in place due to physician error in putting the locking eyelet without proper tensioning resulting in a prolonged procedure.</p> <p>████████████████████ references below relate to row in dFMEA.</p>	<p>Hazards, associated risks, associated benefits</p> <ul style="list-style-type: none"> • Hazards and risks consistent with IFU. • No additional risks identified with this update to clinical evaluation. • Potential benefits of ██████████ suggested in ██████████ literature but primarily associated with this specific application and only theorized. No claims being made on potential clinical benefits for subject device. <p>The clinical significance of the 58.8% cure rate for clinical trial # 2 was discussed further. The Manufacturer clarified that modifications to the device design were made inbetween the phase VI and Phase VII trials and that the Phase VII trial design reflects the currently commercially released design. The modifications included a widening the apical end of the ██████████ by 0.5 cm on each side, or a total of 1 cm. As a result of this dimensional change, the shoulders and eyelets on each side were also moved laterally 0.5 cm. The response further stated that, while the phase VII trial had a higher cure rate, both trials were considered to demonstrate effectiveness because no clinical revisions were required for prolapse. This was considered acceptable.</p> <p>Overall, the clinical evaluation was considered satisfactory.</p>
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				<p>dfMECA: 9 of the 492 identified hazards required justification for approval (in the RMR). These were judged acceptable. The other 483 fell within the acceptable range. 1 identified hazard (#374 – off-label use) was not analyzed as [REDACTED] has no control over this. This is considered acceptable.</p> <p>396. (Critical x Remote) Insufficient dissection of vagina from bladder due to surgical techniques or physician does not follow recommended directions for use resulting in ureter obstruction or dislocation of bladder.</p> <p>407. (Minor x Remote) Unable to load / Anchor not loaded correctly to needle tip and could fall off during the procedure due to physician not properly loading mesh arm & sheath resulting in a prolonged procedure.</p> <p>415. (Minor x Remote) Anchor inserted to the wrong location and may damage peripheral nerves / vessels due to surgical techniques or physician does not follow recommended directions for use resulting in prolonged procedure.</p> <p>416. (Minor x Remote) Anchor is not inserted adequately to the muscle</p>	
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				<p>and doesn't hold due to surgical techniques or physician does not follow recommended directions for use resulting in prolonged procedure.</p> <p>418. (Serious x Remote) Premature anchor deployment due to physician attempts to retract needle and creates bunching resulting in tissue damage; pain.</p> <p>420. (Minor x Remote) Premature anchor deployment due to physician attempts to retract needle and creates bunching resulting in prolonged procedure.</p> <p>450. (Minor x Remote) Unable to load / Anchor not loaded correctly to needle tip (may rotate or separate during placement) due to physician not properly loading mesh arm & sheath resulting in a prolonged procedure.</p> <p>459. (Minor x Remote) Anchor is not inserted adequately to the muscle and doesn't hold due to surgical techniques or physician does not follow recommended directions for use resulting in prolonged procedure.</p> <p>467. (Minor x Remote) Sheath cut out is distorted from first anchor deployment and create difficulty loading the sheath on second arm</p>	
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				<p>assembly due to physician misuse or failure to follow recommended directions for use to press the trigger to load / unload the sheath resulting in a prolonged procedure.</p> <p>In most cases, Risk mitigation is supported by design verification / validation and safe and effective clinical use of [REDACTED]</p>	
<p>[REDACTED]</p> <p>Manufacturer B</p>	<p>[REDACTED]</p> <p>Extract from surveillance technical audit dated 16Jul2012 (SMO [REDACTED])</p> <p>Product C</p>	POP	<p>[REDACTED] conclusion: Risk documentation was found to be acceptable.</p>	<p>Risk analysis documentation was reviewed [REDACTED] and confirmed to be updated with PMS data (last revision June 2012). It was noted that sheath distortion was the most common device related complaint. It was confirmed that a CAPA was raised to change the design of the sheath attachment and the CAPA was under implementation during the audit.</p> <p>Risk documentation was found to be acceptable.</p>	<p>[REDACTED] Clinical Evidence summary Report ([REDACTED] dated 14 Feb 2012)</p> <p>Initial approval of [REDACTED] was based on equivalence with [REDACTED] [REDACTED] are both specifically intended for treatment of pelvic organ prolapse.</p> <p>The updated report summarized the post-market clinical studies for the [REDACTED] and evaluated the clinical data based on other literature.</p> <p>[REDACTED] (Trial [REDACTED]) US, Australia; None in EU; Included other POP devices; A post-market registry for the [REDACTED] for short and long term (2 year follow-up) patient outcomes following the use of [REDACTED] for genital prolapse.</p>

				<p>Longitudinal, 20 center study. Total of 218 patients were implanted with the [REDACTED] 35 with [REDACTED] and 183 patients with [REDACTED]</p> <p>Measure of success: POP-Q stage of 0 or 1 or a Baden Walker grade of 0 or 1 for all prolapse measures. Combined anterior and apical efficacy defined as Grade/Stage ≤ 1 postoperatively was above 2% for visits up to 5-7 months. No efficacy data was available beyond 7 months post-procedure. Two device related AEs were reported. No extrusions.</p> <p>The combined apical and posterior efficacy was 100% reported upto one year. No data was available beyond one year. Longer term efficacy was not determined since [REDACTED] study was initiated(discussed below) Posterior devices were introduced earlier. Hence more Posterior devices in the registry.</p> <p>[REDACTED] study (not a registry)– 28 centers, prospective, non-randomized; US and Europe; multi-phase for the long-term efficacy and safety of [REDACTED] devices. Data collected up to 24 months post procedure. Primary end point – percent of subjects with a POP-Q stage of ≤ 1 at one year post procedure. Confirmed on site that POP-Q scores are available for Phase V EP devices and Phase VII EA devices.</p> <p>Phase V – [REDACTED] 16 sites,</p>
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					<p>139 implants</p> <p>Phase VI – First configuration of the device One year followup; anterior device only</p> <p>Phase VII – Second configuration of the device; Full 2 year followup; anterior device only</p> <p>The difference between the first and second configuration of the device are – slight design changes to the introducer needles, and changes in dimensions to the EA device. No changes in the mesh material, intended use.</p> <p>Phase V – 139 subjects with prolapse \geq Stage II and or apical descent \geq stage II. 24 month data available from 113 patients. Mean followup time was 21.5 months</p> <p>At 24 months, objective posterior wall cure rate (stage \leq1) – 91.5% and apical cure (stage \leq1) rate was 88.2%. QOL questionnaires showed improvements at all time points.</p> <p>Total complication rates – 5.8% 36 subjects experienced 45 adverse events related to the device and or procedure. Most common – Extrusion in 11 subjects (7.9%) Other complications include constipation (2.2%), pain (2.2%), hematoma (1.4%), infection (1.4%), new prolapse (1.4%), recurrence (1.4%) etc.</p> <p>35 subjects with Anterior, apical</p>
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				<p>prolaps >= stage II; 5 european centers 12 month followup; 24 month followup was not conducted due to early phase closure due to a design change identified above.</p> <p>Anatomic support with anterior cure rate of 58.8% and apical cure rate of 90.0% at 12 months QOL significantly improved from baseline. 97% some degree of improvement; 88.2% had lot of improvement compared to baseline.</p> <p>Total intra-operative complication rate was 2.9% 14 subjects experienced 17 adverse events related to device and or study procedure</p> <p>Urinary incontinence – denovo stress - 11,4%</p> <p>Urinary incontinence – worsening stress – 11.4%</p> <p>Extrusion – 5.7%</p> <p>New prolapsed – 2.9%</p> <p>Mfr concluded [REDACTED] safe and effective for prolapsed through 12 months</p> <p>[REDACTED] long term safety and efficacy 142 subjects (anterior prolapse or apical prolapsed >= Stage II), 16 sites, (last followup estimated to be 2012); 24 month followup;</p> <p>125 patient data available for 12 months followup. QOL scores, pelvic floor distress inventory score, pelvic floor impact questionnaire scores all improved significantly.</p> <p>96.8% - some improvement</p> <p>94.4% - moderately, very or extremely satisfied</p> <p>Intra-operative complication rate – 4.2%</p> <p>70 AEs for 49 subjects Extrusion – 5.6% UTInfection</p>
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					<p>– 5.6% Dyspareunia – 4.2% Pain/discomfort – 3.5% Urinary incontinence - 3.5% Urinary retention – 3.5% Granuloma, hematoma etc Rates in line with current labelling. 55 of 70 AEs resolved during the followup period. Anterior prolapse cure rate at 12 months – 87.4% Apical cure rate at 12 months – 95.9% Mfr concluded devices safe and effective for treating anterior prolapse through 12 months 24 month data yet to be analysed.</p> <p>Literature Review Sources: Pubmed, Google Scholar Medline The CER included literature updates between Jan 2011 and Nov 2011 for the [REDACTED] From a total of 21 new articles identified, 1 study and 16 conference abstracts were shortlisted for the literature review The retrospective case series reported 91.7% objective success rate of 91.7% and a subjective success rate of 98.4%. Devices were considered safe and effective at the end of 13 months Based on the post-market clinical studies and the literature reviews, the manufacturer concluded that the [REDACTED] continue to be safe and perform as they are intended to at the end of 2 years.</p> <p>[REDACTED] Observation: No discussion on comparison of mesh devices to non-mesh surgical treatments to establish the utility of the mesh devices for treatment of POP when compared to non-mesh surgical treatments. Other devices are not</p>
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					<p>considered in the literature search.</p> <p>Overall, Reviewed and found to be satisfactory</p> <p>Complaints Data: PMS data review frequency: initially every year and once the device is established, the PMS reports are issued Biannually. PMS reviews include customer complaints, clinical evaluation, IFU review, standard review, and previous PMS report review</p> <p>██████████ Apr 2011- Sep 2011: ██████ devices sold; ██████ complaints; highest complaint rate of 0.03% for component separation, damaged packaging, perforation, pain, and erosion. Overall complaint rate of 0.22%</p> <p>Apr 2010 – March 2011: ██████ devices sold; total of ██████ complaints; overall rate – 0.44% Extrusion – 0.06%, pain – 0.05%, sheath distorted, 0.04%, incontinence 0.03%, erosion – 0.02%</p> <p>Jan 2008-March 2010: ██████ devices sold; ██████ complaints; overall rate of 0.7% Clinical complaints include incontinence-0.08%, recurring prolapsed 0.06%, graft extrusion, 0.06%, infection 0.02%</p> <p>██████████ Apr 2011- Sep 2011: ██████ devices sold; ██████ complaints received; rate of 0.81% Clinical complaints- pain-0.11%, extrusion-0.05%, infection – 0.03%, erosion – 0.03%, dyspareunia, 0.03%, bleeding- 0.03% among others.</p>
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					<p>Apr2010- Mar2011: [REDACTED] devices sold, total of [REDACTED] complaints for an overall complaint rate of 0.5%. Clinical complaints- dyspareunia – 0.04%, pain – 0.02%, UTI – 0.02%, extrusion – 0.02%, prolapsed recurrence – 0.02%, perforation – 0.02%</p> <p>Sep 2008- Mar2010: [REDACTED] devices sold, total of [REDACTED] complaints, overall rate of Clinical complaints – incontinence – 0.14%, pain – 0.1%, and other complaints (<0.04%) include extrusion, UTI, retention, bleeding, dyspareunia etc</p> <p>Device related complaint rates were in the Acceptable ranges as defined in the risk management documentation. The complaint rates are compared to [REDACTED] complaint rates reported in literature for similar devices. The complaint rates are compared to the projected rates as per the risk management documentation and were found to be within the acceptable range. Complaint rates were found to be low and within the acceptable range as defined in the risk analysis. There were 8 adverse event reports within EU since introduction of the Elevate devices.</p>
[REDACTED] Manufacturer B	[REDACTED] Product D	POP	TF to be reviewed in the future as a part of technical file sampling plan		
[REDACTED]	[REDACTED] Product E	UI		[REDACTED] FMEA documents were sampled for this audit- [REDACTED] dFM Revision G for	CER: [REDACTED] No consideration on Suitability of literature and weighting of clinical data. Minor NCR raised.

Manufacturer B	Surveillance Technical file assessment – 19 Oct 2011, SMO [REDACTED]			[REDACTED] for Needle Assembly [REDACTED] Rev D for Sling assembly, Hybrid, Dry Risks associated with Recurrence of incontinence and re-implantation of sling devices are not addressed in the risk analysis. Minor NCR raised FMEA Observation: Risks are not scored for occurrence before and after mitigation of risks	Published data will need to be assessed with respect to its possible contribution and weighting in establishing both the performance of the device in question and its safety. PMS [REDACTED] – Adverse incident rates less than 0.01% of sales. Falls within the acceptable region of risk; PMS data reviewed from 2008 and 2009. PMS reports generated every two years due to familiarity of the product. Two vigilance incidents were recorded in EU from 2006 to 2011.
[REDACTED] Manufacturer B	[REDACTED] Product F	UI	TF to be reviewed in the future as a part of technical file sampling plan		
[REDACTED] Manufacturer B	[REDACTED] Product G	UI	TF to be reviewed in the future as a part of technical file sampling plan		
[REDACTED] Manufacturer C	[REDACTED] Product A	UI	Major Non – conformity raised in 2010 and subsequently closed due to lack of updates to risk management and clinical evaluation via PMS	From Audit report [REDACTED] June 2010 [REDACTED] Reviewing the RA, this is not a dated document therefore we are unable to determine whether the document has been updated or not. RA is at version 1 suggesting it has been	From Audit report [REDACTED] June 2010 [REDACTED] CER requires updating from the currently available 2003 version. Cross checking with the CER this has not been performed The complaints were viewed from 2005 to present

	Product B			<p>never updated. *Electronic record follow up shows date of 21st July 2008 for RA.</p> <p>Risk Management data was reviewed within Legacy Technical Files stated by [REDACTED] to be updated per a Corrective Action Plan referenced in response to last year's Technical Audit (Reference Report [REDACTED], NCR-KR2). The risk management documents viewed were still deficient as noted in the Major Nonconformity issued below; reference [REDACTED] in the Clinical Data Section below.</p>	<p>for two related versions of the products. Only 160 complaints were filed, with 7 or 8 being sheath related</p> <p>Sales data was provided and review did not indicate any obvious trends.</p> <p>From Certificate Renewal [REDACTED]</p> <p>[REDACTED]</p> <p>3 Vigilance incidents related to retention of sheath in patient (1) and vaginal exposure (2) in the last 5 years from [REDACTED] sales</p> <p>[REDACTED]</p> <p>36 incidents in the last 5 years from [REDACTED] sales</p> <p>The ten (10) failure categories</p> <ul style="list-style-type: none"> • Bladder Perforation • Erosion: Urethral Or Otherwise Unspecified • Groin Pain
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					<ul style="list-style-type: none">• In spec/Does not meet customer requirements• Infection• Lower Abdominal Pain• Packaging Inadequate Labeling• Post-Operative Complications (exposure)• Retention of Sheath in Patient• Vaginal Exposure <p>████████████████████</p> <p>34 incidents in the last 5 years from ██████████ sales</p> <p>The eight (8) failure categories are:</p> <ul style="list-style-type: none">• Allergic Reaction• Dyspareunia• Erosion: Urethral or otherwise unspecified• Infection• Lower Abdominal Pain• Packaging Inadequate Labeling• Post-Operative Complications (exposure)• Vaginal Exposure <p><u>Manufactures conclusion for all variants</u></p> <p>Rates in line with that expected from risk assessment.</p> <p>None of the reportable MDV incidents resulted in any further action e.g. CAPA. The incidents continue to be tracked and trended utilising our on-going post market surveillance activities to ensure appropriate action is taken to address any negative</p>
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<p>Manufacturer C</p>	<p>Product C</p>	<p>POP</p>	<p>Manufacturer has open non conformity against risk management system due to review in September 29th 2014 audit</p>	<p>From Audit [REDACTED] May 2013</p> <p>[REDACTED]</p> <p>(Note [REDACTED])</p> <ul style="list-style-type: none"> • RMR (v. 21) replaces ORR (v. 20) and incorporates review contents/ minutes/ R/B Analysis (RBA) conclusion from CER, and overall conclusions into RMR. Each document reviewed now identified by version #. This is very helpful. • Utilized new RM documentation (Risk Assessment Summary - RAS). Nice features include summary of each harm encountered with a Risk Benefit Analysis summary, primary hazards contributing to the harm, actions taken to reduce risk as far as possible, and methods for notifying the user of residual risk. This is a positive step. • The risk analysis (aFMEA) defines risk level as $RPN = S \times O \times D$ (where $S = 4, 6, 8, 9, \text{ or } 10$ and $O = \text{occurrence of hazard with scale from } 0.001\% - 10\% - \text{recorded as fraction}$). The RMR defines risk the same as ISO 14971 = $S \times O$ (where $S = S0 \text{ through } S5$) and $O = \text{occurrence of harm with}$ 	<p>trends or incidents.</p> <p>From Audit [REDACTED] May 2013</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Well written and generally consistent with MEDDEV 2.7.1 with exceptions below. Note: As this was a TF audit, detailed review of the clinical data was not conducted to determine sufficiency to support safety & performance as intended.</p> <p>[REDACTED]</p> <ul style="list-style-type: none"> • States products are manufactured [REDACTED] f mfr is listed, would also list [REDACTED] • Comparison of subject device to other treatment options not obvious. • Benefits of device in comparison to other options not obvious in Risk Benefit Analysis (RBA). <p>[REDACTED]</p> <ul style="list-style-type: none"> • Comparison of subject device to other treatment options not obvious • Benefits of device in comparison to other options not obvious in RBA. Body of text does discuss some statements of benefit outweighing risk from NICE/FDA published guidelines. <p>While review of these files is generally positive, the NC will remain open until additional files can be</p>
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			<p>scale from 0.0004% - 0.1% - recorded in %). Since the RMR does not summarize the ratings from the aFMEA, it is not obvious how the occurrence of harm was calculated and it seems easy to confuse the units between the 2 systems. The causes identified in the aFMEA for a single failure mode (exposure) were reviewed. The ratings and causes were found to be generally consistent with that listed in the RMR but the comparison is not straightforward. The estimate of exposure based on complaints is ~ 2% and the RMR states a frequency of > 0.1%. While this is consistent, there is an order of magnitude difference. It is recommended that if any of the risks have an F5 frequency (> 0.1%), commentary must be included to say what the actual estimate is and discuss it.</p> <p>It is obvious that a lot of thought has gone into the RM procedures, however, having 2 different systems (Risk analysis / RMR) is very complicated and may cause confusion for project teams (and auditors). While this is considered acceptable, it is recommend that the systems be simplified and cross-</p>	<p>reviewed.</p> <p>From Certificate Renewal [REDACTED]</p>
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				<p>referenced as much as possible so it is clear how the ratings were assessed.</p> <p>While review of these files is generally positive, the NC will remain open until additional files can be reviewed.</p>	<p>3 Vigilance incidents related to post-op complications, erosion, vaginal exposure in the last 5 years from [REDACTED] sales</p> <p>Manufactures conclusion</p> <p>Rates in line with that expected from risk assessment.</p> <p>None of the reportable MDV incidents resulted in any further action e.g. CAPA. The incidents continue to be tracked and trended utilising our on-going post market surveillance activities to ensure appropriate action is taken to address any negative trends or incidents.</p>
<p>[REDACTED] Manufacturer C</p>	<p>[REDACTED] Product D indicated for use as a bridging material for sacrocolposu sension/sacr ocolplexy (laparotomy or laproscopic approach(where surgical treatment for vaginal</p>	<p>POP</p>	<p>Manufacturer has open non conformity against risk management system due to review in September 29th 2014 audit</p>	<p>From Audit [REDACTED] May 2014</p> <p>RMR report Rev 2 3/12/13. Summary of changes. Risk/benefit analysis. Clear interactions between RMR and CER.</p> <p>RA Summary. 10/10/13 rev1. Revised for previous format. Harms considered and requiring risk benefit analysis have been reviewed. Methods used to reduced risk has been discussed. Various aFMEA, dFMEA and pFMEA performed.</p> <p>CER referenced. Risks in IFU, vs CER vs RM/RA appear to now be consistent (this was not</p>	<p>From Audit [REDACTED] May 2014</p> <p>PMS surveillance activity is focused on clinical evaluation updates via literature review and complaints. Non conformity raised on clinical evaluation/PMS methods for the files reviewed, including but not limited to objective evidence related to [REDACTED] file.</p> <p>This non conformity was original raised at a previous audit as minor but has been escalated to major due to lack of follow up of the manufacture's corrective action plan in a timely manner. Close out of this non conformity will be reviewed in September 29th 2014 visit.</p> <p>Summary of Non-conformity from report</p>

	vault prolapse is warranted.			<p>the case at previous audit)</p> <p>aFMEA [REDACTED] rev 2 reviewed.</p> <p>[REDACTED] aFMEA [REDACTED] which is not in line with the latest risk SOPs.</p> <p>(Raised as part of non-conformity on Risk management process)</p>	<ul style="list-style-type: none">• The CER for [REDACTED] did not include a sufficient equivalence argument for utilising data from other mesh devices, particularly devices used for transvaginal approach versus abdominal approach.• The CER for [REDACTED] included complications rate tables but it was not clear what devices these rates applied to nor what the significance or acceptability of these were. Reference was included to with/without Burch bladder neck suspension but the significance of this was not clear.• The PMS plan for [REDACTED] refers to clinical investigations. It is not clear whether these are [REDACTED] initiated trials or independent trials nor how these are connected to the data presented in the CER.• The PMS plan for [REDACTED] does not include many proactive techniques for obtaining PMS data on the [REDACTED] the justification for this approach is not sufficiently documented.• The rationale for lack of PMCF for [REDACTED] is not sufficiently justified.
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Annex H: Response from EU counterparts to COEN sent SEPT 2011

	Year of report	No. of reports	Incidents / failure type	No. of implants/vr	Manufacturers selling devices within country	Trends regarding failures/incidents	Advice issued	Other comments	Registers	
Denmark										
SUI	no info	8	mesh eroded in to the vagina and mesh	no info	Ethicon/Johnson & Johnson, Tyco Healthcare, Desarrollo e Investigacion Medica Aragonesa S.L.	6 reports are still under investigation (we received the first report in May 2011), so the root cause is yet to be identified.	no	n/a		
Estonia										
SUI + POP	no info	0	n/a	no info	no info	no info	no	no	no info	
France										
POP	from 2004	69	Erosion, Infection, Rejection, Breaking, pain.	no info	Cousin Biotech, Ethicon, Sofradim Production, AMS, Covidien, Textile High Tech, WOM, Boston Scientific, CL Medical, Europak, Aspide Medical, B Braun Medica	Observed a peak of incidents in 2006 and 2007.	A report from the "Haute Autorité de Santé" (2007), in the framework of reimbursement of these products is available at this address : http://www.has-sante.fr/portail/upload/docs/application/pdf/rapport_devaluation_implant_de_renfort_pour_traitement_de_lincontinence_urinaire_deffort_feminine_et_implant_de_renfort_pour_traitement_du_prolapsus_de_s_organes_pelviens_de_la_femme.pdf	A prospective vigilance enquiry was carried out in 2005 by Afssaps. Results are available at this address : http://www.afssaps.fr/infos-de-securite/Autres-mesures-de-securite/Enquete-prospective-de-materiovigilance-sur-les-bandelettes-par-voie-vaginale(language)/fre-FR	no info	
SUI	from 2001	212	Erosion, Infection, Rejection, Breaking, Migration, Abscess.	no info	Coloplast, Ethicon, AMS, Abiss, Covidien, Sofradim Production, CL Medical, Cousin Biotech, Boston Scientific, Bard, Mentor, Microval, Textile High Tech, Dima Desarrollo E Investigacion Medica, Generic Medical Devices, High Tech Swing, MDSS, Promedon, Aspide Medical, B Braun, Conception Etudes Réalisation d'Implants et d'Ancillaires, MELC, PFM Medical France, TYCO healthcare	Observed peak of incidents from 2004 to 2007	A report from the "Haute Autorité de Santé" (2007), in the framework of reimbursement of these products is available at this address : http://www.has-sante.fr/portail/upload/docs/application/pdf/rapport_devaluation_implant_de_renfort_pour_traitement_de_lincontinence_urinaire_deffort_feminine_et_implant_de_renfort_pour_traitement_du_prolapsus_de_s_organes_pelviens_de_la_femme.pdf	A prospective vigilance enquiry was carried out in 2005 by Afssaps. Results are available at this address : http://www.afssaps.fr/infos-de-securite/Autres-mesures-de-securite/Enquete-prospective-de-materiovigilance-sur-les-bandelettes-par-voie-vaginale(language)/fre-FR	no info	
Ireland										
POP	no info	0	n/a	unknown	Boston Scientific "Pinnacle Pelvic Floor Repair Kit" Ethicon "Proceed"	n/a		FDA Public Health Notification "Serious Complications Associated with Transvaginal Placement of Surgical Mesh in repair of Pelvic Organ Prolapse and Stress Urinary Incontinence" received by the IMB in October 2008 was distributed all Obstetrician Gynaecologists practising in Ireland. The updated FDA notification was also distributed in August 2011.	n/a	No
SUI	no info	0	n/a	unknown	unknown	n/a	no	n/a	No	
Norway										
SUI	2007	1 (Tension free Vaginal Tape-Obturator)	pain in her thigh and backside, and that still after 3 months has the same problems	no info	Johnson & Johnson	no info	no	no	no info	
The Netherlands										

POP	no info	6	Severe pain, re-operation/removal of (parts of) the mesh, problems defecating, dyspareunia, decrease in quality of life for several of the involved women, not being able to work or even perform common daily activities.	Unknown. Figures from 1 manufacturer. Totals vary from 1000-1300 devices sold on the Dutch market annually for this manufacturer alone. In the first half of 2011 the number of devices sold was 426.	Bard Ethicon American Medical Systems Boston Scientific has been mentioned by some surgeons. We did not receive any vigilance reports from this company to date.	Investigation in to cases carried out, focusing on Prolift Pelvic Floor Repair System (Johnson & Johnson). In 2010 we circulated a vigilance enquiry concerning this product. We had the technical documentation assessed by RVM: several warnings, precautions and contraindications mentioned in the IFU, were not mentioned in the risk analysis; validation of sterilisation procedure was insufficient as the validation of the packaging was missing, validation method was missing, re-validation of the packaging was missing and a summary of the results was missing; PMS-procedure was scored as insufficient as it was mainly a passive system describing complaint handling, no pro-active activities were described. Ethicon stated that it is improving its PMS-procedures and more documentation regarding the identified shortcomings was provided. This additional documentation is sent to RVM for further assessment. Conclusions so far are that severe complications arose for several women. Furthermore, it seems that surgeons have become more reluctant to use such mesh for primary surgery and first look at other alternatives. Additionally, we received signals that the long arms of the Prolift seem technically challenging for some surgeons, which may lead to poor positioning of the device and to complications. However, our investigation	no, this is still being considered	In July 2011 the FDA issued an additional warning to the warning issued in October 2008 regarding surgical meshes for pelvic organ prolapse. Additionally, Clinica mentioned a court case against Ethicon of 300 women in the United States.	Yes, recently the Dutch Society for Gynaecology and Obstetrics (Nederlandse Vereniging voor Obstetrie en Gynaecology – NVOG) has initiated the Foundation Registry Complications of Gynaecologic Interventions (Stichting Complicatieregistratie Gynaecologische Ingrepen Nederland). This registry is broader than this device alone.	
SUI	no info	4 (including 1 male sling system, 1 report should have been reported to Belgium)	Pulse arterial bleeding after insertion of the introducer, Deterioration of device before end of shelf life, Patient having a TVTS procedure developed pyelonephritis	unknown	Bard Ethicon American Medical Systems	No, the number of reported incidents is too low for trend analysis.	No		Yes, recently the Dutch Society for Gynecology and Obstetrics (Nederlandse Vereniging voor Obstetrie en Gynaecology – NVOG) has initiated the Foundation Registry Complications of Gynaecologic Interventions (Stichting Complicatieregistratie Gynaecologische Ingrepen Nederland). This registry is broader than this device alone.	
Poland										
POP	no info	0	no info	no info	American Medical System, Inc DePuy Spine, Inc Ethicon Sarl Gynecare Inc Herniamesh S.R.L. Sofradim Production Agency for Medical Innovations GmbH	no	no	n/a	n/a	
SUI	no info	0	no info	no info	no info	no	no	n/a	n/a	
Switzerland										
SUI	2005-2007	20 (4 occurred in Switzerland) Incidents only reported by Ethicon SARL located in Switzerland.	Infection: 4, Urinary retention: 2, Infection: 4 Urinary retention: 2 Erosion: 2 Plastic sheath not retractable: 2 Fever: 2 Death during surgery: 2 Device failure which made implantation impossible: 2 Death due to sepsis: 1 Pain: 1 Ileum perforation: 1 Incontinence not resolved: 1	unknown	As these companies reported incidents and FSCAs, it is assumed they sell devices in Switzerland: Boston Scientific, Johnson & Johnson, Ethicon SARL, Ethicon Inc	no incident reports since April 2007.	No	No	No	
POP	no info	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a	
Sweden										

POP + SUI	2008	1	Uretary injury	unknown	EndoFast Reliant System	no	no	unclear in this case whether the surgery was about prolapsed surgery or stress incontinence surgery	A quality register called Gynop gathers information concerning gynaecological procedures, also including surgery results for prolapse and incontinence operations. MPA has no more information concerning this register.
	2010	5	Stress incontinence	unknown	Prolift Pelvic Floor Repair	no	no	incidents occurred during clinical trial	

Annex I

Information to facilitate discussion of risks and benefits of treatments for women with stress urinary incontinence

(extracted from NICE guidelines CG171 Urinary incontinence: The management of urinary incontinence women – September 2013

<http://www.nice.org.uk/guidance/CG171/chapter/1-Recommendations>)

Risks and benefits up to 1 year			Risks and benefits after 1 year					
Procedure	Continent <1 year	Perioperative events – tissue injury*		Continent >1 year	Erosion	Retention	Voiding dysfunction	De novo overactive bladder symptoms
Retropubic 'bottom-up'	67% to 90% (24 studies)	3% to 6% (29 studies)	2 years	74% to 95% (7 studies)	0% to 4% (4 studies)	0% to 13% (4 studies)	18% (1 study)	0% to 25% (4 studies)
			3 years	81% to 92% (5 studies)	0% (2 studies)	0% (1 study)	No studies	0% to 23% (2 studies)
			5 years	69 to 85% (4 studies)	0% to 1% (4 studies)	0% to 5% (2 studies)	0% to 1% (1 study)	0% to 18% (3 studies)
			7 years	70% to 85% (2 studies)	0% to 1% (2 studies)	No studies	No studies	17% (1 study)
			10 years	56% to 85% (2 studies)	No studies	No studies	No studies	17% (1 study)
Trans-obturator 'outside-in'	60% to 75% (10 studies)	3% to 12% (14 studies)	2 years	80% (1 study)	0% (1 study)	4% (1 study)	No studies	7% (1 study)
			3 years	No studies	No studies	No studies	No studies	No studies
			5 years	No studies	No studies	No studies	No studies	No studies

			7 years	No studies	No studies	No studies	No studies	No studies
			10 years	No studies	No studies	No studies	No studies	No studies
Trans-obturator 'inside-out'	62% to 73% (19 studies)	1% to 3% (14 studies)	2 years	87% (1 study)	No studies	No studies	No studies	No studies
			3 years	75% to 84% (2 studies)	1% (1 study)	No studies	No studies	No studies
			5 years	69% to 89% (2 studies)	1% (2 studies)	No studies	No studies	0% (1 study)
			7 years	No studies	No studies	No studies	No studies	No studies
			10 years	No studies	No studies	No studies	No studies	No studies
Retropubic 'top down'	81% (2 studies)	3% to 7% (3 studies)	2 years	No studies	No studies	No studies	No studies	No studies
			3 years	No studies	No studies	No studies	No studies	No studies
			5 years	No studies	No studies	No studies	No studies	No studies
			7 years	No studies	No studies	No studies	No studies	No studies
			10 years	No studies	No studies	No studies	No studies	No studies
Open colpo-suspension	53% to 94% (10 studies)	0% to 11% (6 studies)	2 years	70% to 86% (3 studies)	No studies	9% (1 study)	No studies	14% (1 study)
			3 years	89% (1 study)	No studies	No studies	No studies	No studies
			5 years	78% to 79% (2 studies)	No studies	No studies	4% (1 study)	25% (1 study)

Autologous rectus fascial sling	93% (1 study)	No studies	5 years	No studies	3% (1 study)	No studies	No studies	16% (1 study)
* Tissue injury includes bladder perforation, vaginal wall perforation, urethral and bladder injury.								