Medicines & Healthcare products Regulatory Agency

CPRD

INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

PART 1: APPLICATION FORM

IMPORTANT

Both parts of this application must be completed in accordance with the guidance note 'Completion of the ISAC Protocol Application Form', which can be found on the CPRD website (https://cprd.com/research-applications).

FOR ISAC USE ONLY	
Protocol No. -	**Submission date -**

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title (Max. 255 characters including spaces)

The long-term impact of vaginal surgical mesh devices in UK primary care: a cohort study in the CPRD

2. Research Area (place '**X**' in all boxes that apply)

Drug Safety	Device X	Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	X	Methodological	
Health Services Delivery			

3. Chief Investigator

Title:	Dr
Full name:	Emily McFadden
Job title:	Departmental Lecturer and Statistical Epidemiologist
Affiliation/organisation:	University of Oxford
Email address:	Emily.mcfadden@phc.ox.ac.uk
CV Number (if applicable):	Submitted in April 2016, do not have reference number.
Will this person be analysing the data? (Y/N)	Y

4. Corresponding Applicant

Title:	Dr
Full name:	Emily McFadden
Job title:	Departmental Lecturer and Statistical Epidemiologist
Affiliation/organisation:	University of Oxford
Email address:	Emily.mcfadden@phc.ox.ac.uk
CV Number (if applicable):	Submitted in April 2016, do not have reference number.
Will this person be analysing the data? (Y/N)	Y

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5. List of all investigators/collaborators

Title:	Dr
Full name:	Emily McFadden
Job title:	Statistical Epidemiologist and Departmental Lecturer
Affiliation/organisation:	University of Oxford
Email address:	Emily.mcfadden@phc.ox.ac.uk
CV Number (if applicable):	Submitted in April 2016, do not have reference number.
Will this person be analysing the data? (Y/N)	Y

Title:	Prof
Full name:	Carl Heneghan
Job title:	
Affiliation/organisation:	University of Oxford
Email address:	Carl.heneghan@phc.ox.ac.uk
CV Number (if applicable):	213_17
Will this person be analysing the data? (Y/N)	N

Title:	Miss
Full name:	Georgia Richards
Job title:	Doctoral researcher
Affiliation/organisation:	University of Oxford
Email address:	Georgia.richards@phc.ox.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	N

Amendments

Title:	Dr
Full name:	Sarah Lay-Flurrie
Job title:	Senior statistician
Affiliation/organisation:	University of Oxford
Email address:	sarah.lay-flurrie@phc.ox.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	Y

Title:	Dr
Full name:	Constantinos Koshiaris
Job title:	Senior statistician
Affiliation/organisation:	University of Oxford
Email address:	constantinos.koshiaris@phc.ox.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	N

[Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator]

6. Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name(s):
Emily McFadden: 12_091R, 13_124R, 14_150R, 15_011A, 16_094
Carl Heneghan: 17_06R

List below the member(s) of the research team who have statistical expertise.

Name(s):
Emily McFadden
Carl Heneghan
Sarah Lay-Flurrie
Constantinos Koshiaris

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):
Emily McFadden
Sarah Lay-Flurrie
Constantinos Koshiaris

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):
Carl Heneghan

ACCESS TO THE DATA

7. Sponsor of the study

Institution/Organisation:	Nuffield Department of Primary Care Health Sciences, Radcliffe University of Oxford
Address:	Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

8. Funding source for the study

Same as Sponsor?	Yes		No	X
Institution/Organisation:	National Institute for Health Research (NIHR) School for Primary Care Research (SPCR)			
Address:	Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG			

9. Institution conducting the research

Same as Sponsor?	Yes	X	No	
Institution/Organisation:				
Address:				

10. Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	

Institutional Multi-study Licence	X
Institution Name	University of Oxford
Institution Address	Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

Will the dataset be extracted by CPRD?

Yes		No	X

If yes, provide the reference number:

11. Data Processor(s):

sing	
sing	

sing area (UK/EEA/Worldwide)	UK
sation name	Nuffield Department of Primary Care Health Sciences, University of Oxford
sation address	Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

[Add more processors as necessary by copy and pasting a new table for each processor]

INFORMATION ON DATA

12. Primary care data (place '**X**' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	

Reference number (if applicable):

13. Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data	X		
HES Admitted Patient Care	X		
HES Outpatient			
HES Accident and Emergency		NCRAS Cancer Registration Data	
HES Diagnostic Imaging Dataset	X	NCRAS Cancer Patient Experience Survey (CPES) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS Systemic Anti-Cancer Treatment (SACT) data	

CPRD Mother Baby Link		NCRAS National Radiotherapy Dataset (RTDS) data	
Pregnancy Register	X	NCRAS Quality of Life Cancer Survivors Pilot (QOLP)	
Mental Health Data Set (MHDS)		NCRAS Quality of Life Colorectal Cancer Survivors (QOLC)	

Area Level Data (place '**X**' in one Practice / Patient level box that may apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (index other than the most recent)		Patient Level Index of Multiple Deprivation Domains	
Practice Level Index of Multiple Deprivation Domains		Patient Level Carstairs Index for 2011 Census	
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland)		Patient Level Townsend Score	
2011 Rural-Urban Classification at LSOA level		2011 Rural-Urban Classification at LSOA level	

Reference / Protocol number (where applicable): discussion of linkage requirements via email with Daniel Dedman 23/07/2019

14. Are you requesting linkage to a dataset not listed above?

Yes		No	**X**

If yes, provide the Non-Standard Linkage reference number:

15. Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes		No	**X**

If yes, provide further details:

VALIDATION/VERIFICATION

16. Does this protocol describe an observational study using purely CPRD data?

Yes	**X**	No	

17. Does this protocol involve requesting any additional information from GPs, or contact with patients?

Yes		No	**X**

If yes, provide the reference number:

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PART 2: PROTOCOL INFORMATION

Applicants must complete all sections listed below
Applications with sections marked 'Not applicable' without justification will be returned as invalid

A. Study Title (Max. 255 characters, including spaces)

The long-term impact of vaginal surgical mesh devices in UK primary care: a cohort study in the CPRD

B. Lay Summary (Max. 250 words)

Urinary incontinence is the unintended leakage of urine during normal everyday activities. It affects one in three adult women, but, despite the wide-ranging impact, fewer than 20% are actively treated. While lifestyle and drug treatments are offered in primary care, surgical care recommended if symptoms persist. Mesh implants have been used for 20 years to treat urinary incontinence (UI) and pelvic organ prolapse (POP) (when one or more of the organs in the pelvis (womb/uterus, bladder or top of the vagina) slip down from their normal position and bulge into the vagina).

In response to recent government enquiries, public attention on the complications after mesh procedures, such as infection, pain, depression, anxiety, loss of sex life, and further surgery, has increased. In 2018, the government put an immediate suspension on the use of surgical mesh for UI in England following recommendations by an independent review of the evidence.

Previous studies have described harms treated in the hospital setting. Our study will use data from General Practitioners (GP) and hospital records to describe complications in patients with UI and POP, in the primary care setting, where patients are treated and managed by their GP long after surgery. We will describe complications in those who have and have not had surgical mesh implants. We will also examine whether complications differ in patients of different ages, weights, with different numbers of children or with the surgical speciality. The results will be used to inform future recommendations for patients intervention choices.

C. Technical Summary (Max. 300 words)

Surgical mesh has been used in urogynaecological procedures to treat stress urinary incontinence (SUI) and pelvic organ prolapse (POP) for the past 20 years. Recent public attention and concerns on complications following mesh in urogynaecological procedures have risen. Such complications may include, pain, infection, depression, anxiety, sexual dysfunction, and further surgery.

The issues with mesh are complex, recommendations differ between national bodies and there is a lack of evidence to inform long term complications.(1) Previous research in the UK has used Hospital Episodes Statistics (HES) data to describe complications (mainly rates of reoperation) related to mesh surgery in the hospital setting. There is a lack of evidence informing comorbidities, workload, prescribing and complications arising in primary care in relation to those who have undergone a procedure.

Therefore this study will use the Clinical Practice Research Datalink (CPRD) linked to HES data to examine the long-term patient outcomes in patients with SUI and/or POP, both with and without surgical mesh implants. Outcomes of interest are grouped into (1) those affecting patient comorbidity and quality of life, such as depression, anxiety and self-harm, and sexual dysfunction, (2) those affecting GP workload, including the number of appointments, referrals, and scans, (3) numbers of prescriptions for antibiotics and for pain relief, and (4) complications. We will describe rates of each outcome stratified by covariates of interest, such as age, body mass index (BMI), parity, those relating to surgery, and other outcomes. We will also fit patient level models (Cox regression for binary variables and, depending on dispersion, Poisson or negative binomial regression for count data) to identify factors that are associated with increased rates of each outcome. Our findings will inform current health policy decisions and shared decision making between patients and clinicians to ensure the safety and management of patients in primary care.

D. Outcomes to be Measured

Four classes of outcomes will be examined, focusing on primary care: comorbidities and quality of life, workload, prescriptions, and complications. These are summarised below, and described in detail in section N (exposures, outcomes and covariates).

Primary outcome:

1. Comorbidities and quality of life:
    1.1 depression/anxiety/self harm;
    1.2 sexual dysfunction;

Secondary outcomes

2.1 Workload - Use of health services:
    2.1.1. number of GP appointments by consultation type (e.g. clinic, surgery, emergency, telephone call, visits etc);
    2.1.2. number and type of referrals, including to psychological services and pain clinics/services; and
    2.1.3 number and type of scans (MRI, CT scans, transvaginal ultrasounds).

2.2 Prescriptions:
    2.2.1 number of prescriptions for antibiotics; and
    2.2.2. number of prescriptions for pain relief (opioids).

2.3 Complications
    2.3.1. hospital admissions; and
    2.3.2 mesh repair/removal surgery
    2.3.3 complications of surgery – bladder problems

E. Objectives, Specific Aims and Rationale

Objectives
To describe long term patient outcomes, in the primary care setting, in patients with SUI and/or POP, both with and without surgical mesh implants.

Aim 1:
To describe rate of the outcomes, listed in section D and described in detail in section N, in patients who have received mesh insertion surgeries and those who have not.

For each outcome (the number of appointments, referrals, prescriptions, diagnoses etc.), we will describe the rate in each calendar year since diagnosis. Where relevant, rates will be stratified by covariates of interest, including age groups, BMI, ethnicity, recent childbirth, year of surgery and surgical speciality of the consultant.

Aim 2:
To identify factors that are associated with increased rates of patient outcomes, listed in section D and described in detail in section N. For each outcome, we will fit patient-level models (Cox regression for binary variables and, depending on dispersion, Poisson or negative binomial regression for count data) to examine factors associated with rates of the described outcomes Factors will include covariates of interest, including age groups, BMI, ethnicity, recent childbirth, year of surgery and surgical speciality of the consultant.

Rationale
Recent research has described short term outcomes in the hospital setting, but no studies have examined outcomes over longer time periods or outcomes relevant to primary care. We also wish to
identify factors associated with increased rates of outcomes. Our patient and public involvement (PPI) work has demonstrated that this is an area of interest to patients. This study will aim to address this gap in the evidence.

F. Study Background
What's the problem?

Surgical mesh implants have been used in a significant number of patients in the last 2 decades to repair weakened or damaged tissue. They are mainly used in urogynaecological procedures to treat SUI and POP. There have been concerns, however, about high rates of complications and harms. Complications may include, pain, infection, depression, anxiety, sexual dysfunction, mesh erosion and further surgery (2–5). More than 100,000 women are suing manufacturers globally due to the accumulating reports of harms attributed to mesh (6–8). Pressures from patient advocacy groups, and media exposure on the reports of harms and the exposure of failings in market approvals of mesh devices led the UK government to suspend transvaginal mesh devices (9). However, evidence is still lacking on the long-term health outcomes in primary care for patients who receive surgical mesh devices.

What's the evidence-base?
In 2005, NICE guidance stressed the need to inform women of the lack of long-term outcome data while a Cochrane review on surgery for SUI recommended studies to be conducted with longer follow up (10,11). Two years later, a Cochrane review on POP in women reported insufficient evidence to support practice concluding there is an urgent need for adequately powered trials (4). No changes were found in the subsequent Cochrane review updates (12–14).

Updated Cochrane reviews of mesh or grafts compared with native tissue have found mesh to be associated with concerning complications such as higher rates of repeat surgery, mesh exposure, bladder injury and de novo SUI (15). The US FDA reclassified mesh in 2016 from a moderate to a high-risk device (16). An 8-year study of over 92,000 women in the UK following vaginal mesh procedures for SUI in Hospital Episode Statistics (HES) data found 5.9% of women were readmitted at least once within 5 years and complication rates were higher (9.8%) in those who had had concomitant procedures (3). A similarly sized study, also in HES, found that the mesh removal rate increased from 1.4% at 1 year, to 2.7% at 5 years to 3.3% at 9 years (17). Transvaginal mesh products for POP have been approved on the basis of weak evidence(18). Scottish data on the adverse events after mesh and non-mesh surgeries for SUI and POP, concluded further research on long-term outcomes would be beneficial (19).

The accumulating evidence on harms led to a UK Government independent inquiry, ordered by the previous health secretary, Jeremy Hunt (20). The interim recommendation of this report recommended surgeries using transvaginal mesh should be banned until steps have been taken to mitigate the risk to patients. Recent NICE guidance recommended mesh could be used in the NHS once certain conditions were met, although it is subject to a period of "high vigilance restriction," that incudes a new requirement for all mesh procedures and any related complications to be recorded in a national database (1).

From examining the current evidence on surgical mesh devices, it is evident that the evidence on long-term outcomes is unclear. Our study aims to inform the evidence for complications beyond readmission and address patient calls for more information on the harms and safety of surgical mesh devices.

G. Study Type
Descriptive study (aim 1) and exploratory/hypothesis generating (aim 2).

H. Study Design
Open cohort study

I. Feasibility counts
An early feasibility count for this project done in May 2018 noted that there were 6673 women with codes for a mesh device in HES data between Jan 2005 and May 2018.

A recent count of all women with acceptable patient data, registered at up-to-standard CPRD Gold practices between Jan 2005 and June 2019, with codes in CPRD for SUI and/or POP gave approximately 285,000 women, of which, based on the earlier count, we estimate that about 6500 of them will have had mesh surgery.

J. Sample size considerations
Our study aims are descriptive and hypothesis generating. The feasibility count based on HES codes estimated that approximately 6500 women had codes for mesh surgery for SUI (compared with over 200,000 women who have a code for SUI and/or POP).

We estimate that the precision of the rates of our primary outcome in the table below. As it is not likely that all 6500 women will be contributing data simultaneously, we have included some additional sensitivity analyses around the expected number of women.

Outcome	Expected prevalence	Estimated N	Estimated SE	Estimated 95% CI
Depression	10% (21)	6500	0.37	9.3 to 10.7%
		3000	0.55	8.9 to 11.1%
		1000	0.95	8.1% to 11.9%
Sexual dysfunction	14% (22)	6500	0.43	13.1 to 14.8%
		3000	0.63	12.8 to 15.2%
		1000	1.10	11.8 to 16.2%

K. Planned use of linked data (if applicable):

Linkage to the Hospital Episodes Statistics data is requested. This data is necessary for defining the primary exposure of interest, insertion of a mesh device. It will also be used to obtain outcome data on further surgical procedures involving the device, such as repair and removal, and for outcomes such as hospital admissions and scans (MRI, CT scans, transvaginal ultrasounds).

Linkage to the Index of Multiple Deprivation is requested. Socioeconomic status may be considered a potential covariate of interest and thus data is required to adjust analyses accordingly.

ONS death linkage is requested to ensure follow-up is censored at date of death.

As the data is GOLD data, linkage to the pregnancy register is requested. Previous pregnancy history is a potential covariate of interest. We believe linkage will provide the most reliable information.

L. Definition of the Study population

This is an open cohort of adult female patients (≥18 years of age), registered at "up to standard" CPRD practices, with linkage, and deemed to have "acceptable" patient records. All patients will have a diagnostic code in their CPRD records for either SUI and/or POP (see appendix A for code list). All analyses will be stratified by diagnosis.

Follow up

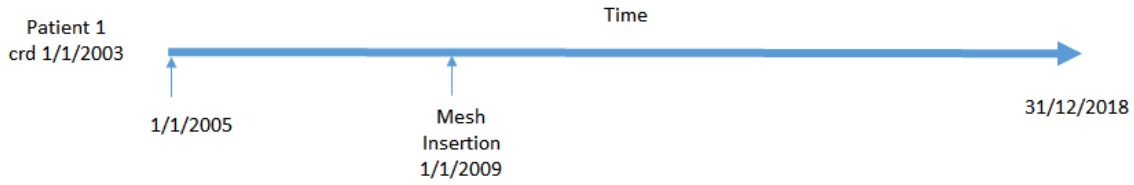
Eligible patients will be registered with the practice for a minimum of 12 months prior to study entry, to ensure adequate recording of baseline covariates. Eligibility will be defined using all available date prior to entry date. Patients who have mesh insertion surgery during follow up will contribute data to both the "unexposed" group (no insertion) and then the "exposed" group (mesh insertion), as described below.

Study index date for each patient will be the latest of the following dates: practice up-to-standard date, date of 18th birthday, date of current registration with the practice plus 12 months, and study start date (1/1/2005), date of diagnosis with SUI or POP, and where applicable, date of mesh surgery.

Patient records will be censored at the earliest of the following dates: study end date (date of last available linked data), date of last upload of practice data, date of death, transfer out date, or where applicable date of censoring (those without mesh –date of mesh insertion, those with mesh insertion already - date of mesh removal surgery).

These dates are illustrated in figure 1 below.

Figure 1:



For example, patient 1, born in 1975, is registered at a practice that became up to standard on 1/1/1990, whose current registration date was 1/1/2003, and was still registered at the date of last upload of practice data (31/12/2018). This patient had a mesh insertion on 1/1/2009. They would contribute data to the patient group without mesh insertion from 1/1/2005 until 1/1/2009 (mesh insertion date). They would contribute data to the patient group with mesh insertion from 1/1/2009 (date of mesh insertion) until 31/12/2018.

M. Selection of comparison group(s) or controls

The comparison group will consist of patients who have a diagnostic code for either SUI and/or POP, but have not had surgery involving a mesh device.

As described in section L, patients who start out in this unexposed group, can later enter the exposed group if they have mesh insertion surgery during eligible follow-up. Their contribution to the unexposed group would be censored at the date of insertion.

N. Exposures, Outcomes and Covariates

Exposure:
First surgery for the insertion of a mesh device, defined using relevant diagnostic codes. Codes are based on previous research in HES data, (see Appendix for list). The different types of mesh can include: polypropylene, polypropylene composites, and other synthetic and biologically derived mesh. The mesh devices may also be coded as a graft, a patch, sling, tape, biomesh, a vaginal support system or a tension-free vaginal tape.

Secondary exposure:
Patients who have previously received surgery for the repair, renewal and removal of a mesh device will be analysed separately. We will use published codelists (3). Further surgery is also analysed as an outcome.

Outcomes

	Outcome variable	**Variable type**	**Dataset**	**Description**
1	Comorbidities and quality of life:			
1.1.1	depression/anxiety/self harm;	Binary	CPRD	Presence of diagnostic code or drug prescription
1.2	sexual dysfunction;	Binary	CPRD	Presence of diagnostic code
2.1	Workload - Use of health services:			
2.1.1	number of GP appointments by consultation type (e.g. clinic, surgery, emergency, telephone call, visits etc);	Count	CPRD	Consultation file
2.1.2	number and type of referrals, including to psychological services and pain clinics/services; and	Count	CPRD	Referral file, read codes
2.1.3	number and type of scans (MRI, CT scans, transvaginal ultrasounds).	Count	CPRD	Referral file, read codes
2.2	Prescriptions:			

2.2.1	number of prescriptions for antibiotics; and	Count	CPRD	Drug prescription
2.2.2	number of prescriptions for pain relief (opioids	Count	CPRD	Drug prescription
2.3	Complications:			
2.3.1	hospital admissions; and	Count	HES/CPRD	Opcs codes/read codes
2.3.2	mesh repair/removal surgery	Binary	HES/CPRD	Opcs codes/read codes
2.3.3	complications of surgery - bladder problems	Binary	CPRD	read codes

Covariates
Covariates of interest are as follows:

- Age (estimated from year of birth. categorised into 5 year groups)
- BMI (latest value in the year before start date, categorised into <18.5, 18.5-24.9, 25-29.9, >=30 kg/m2)
- Deprivation (categorical)
- Ethnicity (divided into categories (“white”, “Asian”, “black”, “other”/”mixed”, missing)
- Region divided into categories (aligning with the 10 SHAs of England (as we are using only linked data)).
- Factors relating to childbirth (recent childbirth, within 1 year of mesh surgery; number of pregnancies)
- Year of surgery
- Surgical speciality of consultant performing the procedure

O. Data/ Statistical Analysis

Data management and analyses will be carried out using Stata. All analyses will be grouped into women with a code for SUI or for POP.

Aim 1
For each outcome, we will summarise crude rates by year of follow-up in tables and graphically. We will examine rates of outcomes in those who have and have not had mesh surgery (denominator). We will then examine rates by the other listed outcomes and the listed covariates (e.g. age groups, recent childbirth, year of surgery etc.). Where appropriate we will use statistical tests (e.g. Chi squared tests) to formally test associations of the listed covariates on testing rates.

Aim 2: To identify factors that are associated with increased rates of patient outcomes.
Binary outcomes will be analysed using Cox’s proportional hazards models, to allow for varying lengths of follow-up. Covariates of interest will be included in the model.

Count data will be modelled as a Poisson distribution, after testing for overdispersion. If data are over dispersed, we will use a negative binomial regression model to assess the relationship between covariates and each outcome. The outcome of the model will be the number of appointments/referrals/tests/ prescriptions on record following study entry, with the log person-years of follow-up used as the offset term. The model, therefore, estimates the natural log rates of each outcome (appointments/referrals/prescriptions), and covariate effects are log incidence rate ratios (IRRs).

P. Plan for addressing confounding

This study is descriptive and hypothesis generating rather than hypothesis testing.

Aim 1:
We will explore whether rates of outcomes vary by strata of covariates of interest.

Aim 2:

We plan to use multivariate adjustment to examine the adjusted association between outcome rates and covariates of interest.

We are aware that our descriptive comparisons between patients who did and did not have mesh devices fitted may be subject to confounding by indication. We still feel that this comparison is worth including to give some indication of rates of each outcome in a group of patients who may have been eligible for a mesh device. This limitation will be discussed in any research output.

Q. Plans for addressing missing data

Data for age will be complete as a requirement for study entry (patients are aged ≥18 years).

For the assessment of clinical diagnosis/disease in individuals, we will assume that absence of any relevant medical read code in the clinical record means true absence of disease; similarly for childbirth. Numbers of consultations, referrals and prescriptions will not be missing, as the absence of a code will be interpreted of that variable. This strategy may mean that we underestimate the prevalence of sexual dysfunction, this will be acknowledged as a limitation. Anxiety/depression/self harm may also be underestimated; we plan to use published code lists that include both diagnostic and prescription codes to minimise this and will acknowledge this limitation in any publications.

Ethnicity may have high levels of missingness within CPRD data but using HES data as well should reduce this. We will use an indicator for missing data.

The covariate BMI is likely to have high levels of missing data. Our study period is from 2005 onwards, when the Quality Outcomes Framework gave incentives for recording BMI. This should hopefully mean missing data is less prevalent than for earlier time periods. Analyses in aim 1 will be presented as complete case. We will also compare the BMI/obesity distribution of our cohort to population-based data. If the necessary assumptions are met (23), we will use multiple imputation methods for aim 2.

R. Patient or user group involvement

1. Protocol development, aims and methods

We had a conference call with a patient representative, Kath Sansom, the founder of a leading patient advocacy group, Sling The Mesh. This campaign has more than 7,000 members with approximately two thirds of her members having a mesh device to treat incontinence and one third to treat prolapse. There is a growing number of members joining who are experiencing complications after hernia repairs and a smaller proportion of patients who have had rectopexy or biological mesh.

During this conference call, we discussed the protocol, research question, objectives and outcome measures of the study to ensure they were patient-specific, appropriate and relevant. Kath provided feedback and insight into each component particularly around the importance of capturing the impact on mental health, the use of pain services and the unnecessary use of scans, such as MRI and CT's, as a transvaginal ultrasound are more appropriate for examining patients with transvaginal mesh complications. We also discussed patient demographics and the differences she's observed between ethnic groups. Finally, we discussed the importance of research dissemination and our current dissemination plan which she contributed to and advised us on. Notes from our discussion were typed up and emailed around to key stakeholders who are members of the Sling The Mesh campaign. This provided further contributions to our final protocol design.

CH is a member of the UK government's All Parliamentary Party group on surgical mesh. He regularly attends parliament sessions and has consulted with over 100 women about the harms and the problems faced. This direct policy engagement and patient involvement has also informed the development of the protocol.

2. Data analysis (results, discussion and conclusion)

After the data is analysed, we plan to present the raw findings to Kath and key stakeholders from the Sling the Mesh campaign. This PPIE session will be used to determine the key patient-specific findings. We will also re-discuss our dissemination strategy including the development of plain English summaries.

3. Dissemination (reflections and critical perspective)
PPIE sessions will be used throughout each phase of this study and any advice and guidance generated from these sessions will be adopted.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

The results will be submitted for presentation at academic conferences and scientific journals.

We will also produce a media release and distribute lay summaries via: Twitter (~10,000 followers cumulatively), the Sling The Mesh social media sites, our Department's website, local Patient Participation Groups (PPGs) and via local Clinical Commissioning Groups (CCGs).

Our findings will be disseminated to the MHRA, NHS England, Public Health England, Royal Colleges particularly the Royal College of General Surgeons and other health professionals who treat patients pre and post surgical mesh implants (Royal College of Nursing and Midwifery, Associations for Physios and Psychologists), and to parliamentary officials. We will provide a direct report to the All Parliamentary Party group on surgical mesh and seek to present the results in the Houses of Parliament.

Conflict of interest statement:
EM and GR have no conflicts of interest.

CH has received expenses and fees for his media work. He holds grant funding from the NIHR, the NIHR School of Primary Care Research and the NIHR Oxford BRC. He has received financial remuneration from an asbestos case and given free legal advice on mesh cases, and received income from the publication of a series of toolkit books published by Blackwells. On occasion, he receives expenses for teaching EBM and is also paid for his GP work in NHS out of hours. He is Editor in Chief of BMJ Evidence-Based Medicine, clinical advisor to the APPG on Surgical Mesh and an NIHR Senior Investigator. CH is also Director of CEBM and Programs in EBHC CEBM jointly runs the EvidenceLive Conference with the BMJ and the Overdiagnosis Conference with some international partners based on a non-profit model.

T. Limitations of the study design, data sources, and analytic methods

Where feasible we have planned to use code lists/strategies based upon published studies, including work done by experienced colleagues in our Department. Much of our outcome data should be complete (see section Q above), however we are likely to under ascertain data on sexual dysfunction as symptom data is known to not be well recorded, and depression has been shown to be recorded as "low mood".

Mesh surgery should be well recorded in HES data, but there may be some misclassification of exposure status if patients have mesh insertion surgery prior to registering with the CPRD practice contributing data, however given it is relatively major surgery, it may be coded retrospectively. We will also examine codes for repair/removal of mesh devices to define study exit, so if patients have had later surgery coded as such, this should be possible to assess.

It is plausible that different mesh devices may have different complication rates however we cannot describe this as information on the specific type of mesh device used is not available.

Analyses in aim 2 are subject to the usual caveats for statistical modelling based on observational data, and to the usual limitations of routinely collected data for research.

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List of Appendices

ISAC_codelists_Mesh.xlxs –
Codes lists for inclusion, exposure (mesh surgery), primary outcomes of depression, anxiety and self-harm and sexual dysfunction.

Amendments

Aim 1 - Rates will be examined stratified into those with and without a previous history of the outcome of interest
Aim 2 -
To clarify - outcomes are a new occurrence or diagnosis after study entry, therefore analyses will also be done by subgroups examining the risk of the outcome, stratified into those who have a previous history of the outcome of interest.

We wish to make a minor amendment to our protocol (19_167) entitled "The long-term impact of vaginal surgical mesh devices in UK primary care: a cohort study in the CPRD". After discussion, we have decided we no longer wish to study the covariate "number of pregnancies", for which we were requesting data from the pregnancy register. It fits under the following example given in the guidance:

> *"Not using linked data which are part of the approved protocol (applicants should justify how this will not significantly impact on the study. Where not using linked data is likely to have a significant impact, this will require a major amendment);"*

We feel that this covariate does not directly relate to our primary study aim. While the number of pregnancies likely impacts on whether or not a woman has SUI or POP, we do not feel that its possible impact on the rates of depression or sexual dysfunction is our primary interest. It is not a factor that guidance on the use of mesh devices is likely to consider