Test-Case Protocol

Version 2, July 31, 2020

R2-B5 -
Synthetic Mid-Urethral Slings for Stress Urinary Incontinence in Women

Protocol

National Evaluation System for health Technology coordinating center (NESTcc) ID

Number: [R2-B5]

Lead Principal Investigator: [Michael Matheny, MD, MS, MPH]

Sponsor: [FDA]

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PROTOCOL SYNOPSIS

Protocol Number:	R2-B5
Protocol Date:	07/31/2020
Test-Case ID/Title:	Synthetic Mid-Urethral Slings for Stress Urinary Incontinence in Women
Investigator(s):	Michael E. Matheny, MD, MS, MPH
Study Description:	This project seeks to better understand the safety of mesh mid-urethral slings used for stress urinary incontinence by leveraging electronic health record data. The FDA intends on incorporating these data into its growing portfolio of evidence in order to help support regulatory decision making on level of risk for these procedures and recommendations around use of synthetic mesh for this indication. This study has the potential to increase medical knowledge regarding these devices. A detailed schematic describing all assessments is included in **Section 6, Study Procedures**.
Summary and Objectives:	The objectives of this project are to assess the capacity of routinely collected electronic health record data to be used to evaluate mid-term (>1 years) to long-term (>2 years) adverse events following transvaginal synthetic surgical mesh implantation (mid-urethral slings) for female stress urinary incontinence (SUI).
Study Design:	This project will be a multi-site retrospective cohort analysis of patients undergoing surgery for the indication of stress urinary incontinence for mid-term outcomes (1 year and greater) and long-term (2 years and greater) among both those with and without trans-vaginally placed synthetic mid-urethral slings (MUS).
Endpoints:	This project seeks to provide a proof of concept for post-market medical device surveillance utilizing electronic health record data, in a use case of substantial public health safety interest to the FDA, patients, and health care providers: mid- and long-term adverse outcomes related to synthetic surgical mesh implantation for stress urinary incontinence. In pursuit of this goal, this proposal will: 1) Assess data element availability among key covariates and exposures among patients undergoing surgery for stress urinary incontinence. 2) If data are available, to assess rates of outcomes of re-operation for SUI, mesh erosion, re-operation for mesh revision or removal, chronic pain either as a new or worsening pain or requiring re-operation and voiding symptoms either as a new symptom or requiring re-operation, each with extended surveillance windows after surgery. 3) Provide a report of additional data elements important to conduct future device post-market surveillance in implantable devices for this indication, extrapolating to other device domains.

4) Lastly, if the data quality and volume are sufficient, we will develop a risk prediction model for the risk of the each of the outcomes stated above among patients receiving mesh for SUI.

Statistical Methods: Each of the outcomes, exposures, and covariates will be summarized in aggregate for each site and a summarization and report will be provided to characterize the data at each site. Stratified reporting of those receiving surgery for SUI with synthetic mesh overall, SUI with synthetic mesh implantation by surgical approach, and SUI without mesh will be performed.

Next, if the characterization of the data is sufficient for the task, we will pursue a Cox proportional hazards model analysis, with each of the outcomes assessed from the time of the surgery as a time-to-event. We will censor the time-to-event analysis with death or loss to follow-up, defined as a time period >2 years from last applicable encounter of primary care, Obstetrics & Gynecology, or Urology. The models will first be developed at each institutional separately using LASSO Cox to predict time to event for each of the outcomes of interest. We will use the variables retained in any of the individual site models, and develop a Cox model using the method described by Lu and colleagues (WebDISCO) that uses a distributed analysis approach to obtain an exact model solution without sharing case level data (only intermediate and aggregate model coefficients and matrices)[1]. This method is being used to protect patient data by processing it at the local institutions and only sharing intermediate modeling statistics (aggregates) between sites.

Because bootstrapping combined with the distributed analysis method would be computationally intensive, we will utilize 10-fold cross validation across all sites for internal validation of the risk model. We assessed overall discrimination using Harrell's concordance statistic (C-statistic). To provide calibration assessments, we will also evaluate the model at fixed time points of 1 year and 2 year for each outcome using the AUC and the Estimated Calibration Index (ECI). The ECI looks at the squared difference between the predicted probability and an estimated observed probability, ranging between 0 and 100, with 0 meaning perfect calibration. Additionally, we will graphically analyze calibration by investigating the smoothed observed-to-predicted probability plot.

Target Population: All women aged 18 or greater undergoing transvaginal surgery for stress urinary incontinence with or without mid-urethral mesh sling implantation are eligible for inclusion in the EHR data. Determination of the appropriate mesh exposure during surgery will be determined through administrative CPT procedure codes, as defined in the appendix. No exclusions will be applied based on race or ethnicity. As a separate sensitivity analysis to reduce potential lack of outcome ascertainment, we will exclude all patients that do not also have continuity of care within the data site, defined as requiring at least one outpatient medicine specialty or relevant (Obstetrics & Gynecology, Urology) sub-specialty encounter in the 12 months prior to implantation. For this sensitivity analysis, we will also exclude patients with prior pelvic organ prolapse or stress urinary incontinence surgeries. As an additional comparator population, we will

	identify all those who underwent a procedure for SUI but did not receive mesh implantation.
Description of Sites/Facilities:	The Participating Sites for this Study include Vanderbilt University Medical Center, Lahey Hospital & Medical Center, Mayo Clinic, Weill-Cornell, and Yale New Haven Health System. In addition, as a data quality validation check, we will have access to a manually collected and curated 3,472 patient case series at Mayo Clinic from 2002 to 2012 of patients that underwent surgery for incontinence[2]. For the routine EHR data sources, the valid dates will be from 2010 to the most recently available data. As a preliminary assessment of data volume, each site queried their data for CPT 57288 sling operation for stress incontinence. VUMC had a total of 6,106 from 2010-2018, and an average of ~500 cases a year for the last 4 years. Mayo Clinic had a total of 5,413 cases from 2010-2018, and an average of ~500 cases a year for the last 4 years. Weill-Cornell had 887 cases from 2010 to 2019, and an average of 150 procedures a year over the last 4 years. Yale New Haven Healthcare System has data from 2013-2018, and about 170 procedures in the most recent 6-month period. Lahey Clinic had 108 surgeries in 2018, and an average of 84 procedures a year over the last 4 years.
Description of Study Intervention:	This is an observational study design, and there are no direct interventions for patients, thus a Data and Safety Monitoring Plan is not required, and a Data and Safety Monitoring Board is not required.
Study Duration:	1 year, Start Date 02/17/2020, End Date 03/15/2021.
Duration of Data Captured:	2010-2019 in EHR Data

1. INTRODUCTION

1.1 RATIONALE & BACKGROUND

Urinary incontinence, defined as involuntary loss or leakage of urine, is a common problem that affects women more often than men, with prevalence increasing with age[3]. There are several types of urinary incontinence, with distinct differences in pathophysiology between men and women[4,5]. Incontinence in women is typically related to dysfunction of the bladder or pelvic floor muscles through functional or mechanical changes over time resulting from pregnancy, childbirth, in menopause, or other conditions[5]. There are two main subtypes of urinary incontinence, stress and urge, and a third type that can be defined as mixed symptoms of both[6]. In urge incontinence, leakage occurs with a sudden intense need to void, and in stress incontinence, leakage is associated with physical exertion, coughing, sneezing, or other activity.

Urge incontinence mainly involves bladder dysfunction, either detrusor overactivity, poor detrusor compliance, or bladder hypersensitivity. This is important because treatment pathways are distinct as well. Unlike urge incontinence, two common mechanisms for stress urinary incontinence (SUI) are either urethral hypermobility resulting from loss of support of the bladder neck and urethra, and weakness of the urinary sphincter itself[5]. The hammock hypothesis is supported as the pathophysiological explanation for SUI associated with hypermobility[7]. Weakness of the sphincter itself can occur after trauma, repeated surgeries, neurological disease, aging, or systemic muscular atrophy. The Integral theory expands on the hammock hypothesis to include an understanding that stress and urge symptoms may have multiple reasons for generating a lax vagina, which impairs the mediation of muscle movements involved in

bladder neck function as well as inducing urgency through stretch receptors in the urethra and bladder neck[8]. Although all SUI treatments are used for both types, they are more successful among those with urethral hypermobility, than for isolated sphincter weakness[9].

As noted above, SUI is a common condition among women, and negatively impacts patient quality of life, with an estimated 50% of patients experiences some symptoms during their lifetime[10]. Because of the impact of SUI, many women seek treatment for these symptoms, and first line treatments of symptoms includes lifestyle changes, fluid intake restriction, pelvic floor exercises, and vaginal pessaries[4]. When these are inadequate, implantation of a mesh mid-urethral sling is a recognized minimally invasive surgical treatment for SUI[11,12].

An estimated 1 in 5 women will undergo surgery for pelvic organ prolapse (POP) or SUI by age 80 in the US, and approximately 260,000 underwent surgical repair for SUI in 2010[13,14]. While there are multiple types of surgery, the most common is a trans-vaginal approach that uses one of four routes to conducting the procedure, depending on circumstances and provider and patient preferences: Retro-Pubic (RPMUS), Trans-Obturator (TOMUS), Single Incision (SIMUS), and Adjustable Sling (AMUS). Surgical implantation of mesh to create mid-urethral slings (MUS) to relieve these symptoms has been reported to have one-year curative results for TOMUS from 62-98% and for RPMUS from 71% to 97%[11,15]. Older studies have shown lower success rates for SIMUS vs RPMUS and TOMUS[16].

Across all approaches, these implanted medical devices have also been shown to have a number of adverse outcomes, including chronic pain[17], urethro-vaginal fistula[18], voiding dysfunction[19,20], and mesh erosion[21,22]. Voiding dysfunction can develop in 3-30% of patients after RPMUS and 0-16% after TOT[23]. Because of these adverse outcomes, reoperation rates can approach 8-9%[24]. Overall, these procedures were thought to have reasonable success and adverse event profiles for outcomes out to one-year post-operation, but data beyond this window was sparse.

However, by the mid-2000's, a growing number of adverse event reports had been submitted to the MAUDE FDA database related to trans-vaginal synthetic mesh products used for these indications. During 2005-2010, MAUDE received 1371 reports of injury, death, and malfunction of mesh for SUI treatment, related to mesh erosion, pain, infection, recurrence of urinary symptoms, and organ perforation, along with a 5-fold increase in MAUDE reporting rates in 2008-2010 compared to 2005-2007. While these numbers increased scrutiny surrounding these devices, a lack of denominator data and a reliance on voluntary reporting that is sensitive to FDA and press scrutiny limit the interpretability of these findings.

Risk assessments around synthetic surgical mesh for SUI remains uncertain for some outcomes extending beyond one year[25]. Dr. Sedrakyan and colleagues evaluated a New York State prospective registry (SPARC) that included all surgeries and evaluated 41,604 women undergoing mesh implantation for pelvic organ prolapse or stress urinary incontinence. Among the 22,252 women undergoing surgery for SUI, 1.6% of them had mesh erosions that required intervention[22]. In one UK study, overall re-operation rates were only 3.2% among mid-urethral sling procedures for SUI after a median 2.8 years of follow-up[26]. In a private US claims database, the cumulative re-operation rate was 14.5% after a median 9 years of follow-up[27], with sling revision/removal at 3.7%[28]. Other small studies in non-US populations have shown low rates of long-term complications (1-3%)[29]. A recent UK study among 95,057 women and a median follow-up time of 5.5 years found that risk of re-operation was 2.6% at 1 year, 5.5% at 5 years, and 6.9% at 9 years[30]. More specifically, mesh removal rates were 3.3% at 9 years in this population. Another UK study among 92,246 patients with first time mesh implantations for SUI found a 5-year complication rate of 9.8%[31]. A Canadian study of 59,887 women found ~3.5% may require mesh removal or revision within 10 years of initial surgery[32].

There have also been some systematic reviews and meta-analyses done attempting to further understand the complications in this population. In 2015, a systematic review of studies with a follow-up of 36 months for TOMUS and 60 months for RPMUS were searched and studies comparing the two were

included (49 studies, 11 RCT, 38 retrospective cohort studies)[33]. The studies had a complication rate of 193% for RPMUS and a complication rate of 23.8% in TOMUS surgeries. The two approaches had similar objective cure rates, but TOMUS had a lower subjective cure rate than RPMUS. In 2017, a review was published evaluating 11 RCTs and 5 non-RCTs evaluating the long term efficacy and safety of MUS in women[34]. There was a total of 1,200 patients across 11 RCTs with individual surgical approach populations in each trial being in the 30-299 range. Ascertainment for the RCTs were good and showed no safety or efficacy differences between approaches but were limited in size, and the non-RCTs were similarly limited in size (5206 patients across 5 studies). The most recent review, in 2019, evaluated a total of 175 RCTs with 21,598 women, and noted that most studies had high or unclear risk of bias across all Cochrane domains[35]. A network metanalysis was done from 105 trials that reported cure and 120 trials that reported improvement of symptoms, and across the 4 common surgical approaches for MUS. The key findings from this meta-analysis was that RPMUS, TOMUS, traditional sling, and open colposuspension were more effective than other procedures for SUI, but that data on long term effectiveness and adverse events were limited, particularly around comparison between MUS and non-MUS procedures. Other relevant articles are referenced here as well, but almost all of these also cite limitations in sample size, data bias collection, and evidence limitations[36-41].

The FDA is very interested in measuring the risk of mesh use for SUI for longer outcomes >1 year within electronic health record data, which are collected for routine care and can be accessed for a variety of surveillance activities. For this reason, NESTcc was approached by the FDA to engage in a collaborative consortium to pursue these concerns, and an RFP was released to study this within an electronic health record environment in which it is hoped that longer term outcomes can be ascertained. Multiple academic medical centers, including Vanderbilt University Medical Center, Yale New Haven Health System, Weill-Cornell, Mayo Clinic, and Lahey Hospital & Medical Center, were recruited to collect and analyze patient data regarding mesh implantations for SUI for the outcomes of re-operation, mesh erosion, all-cause chronic pain, and continued voiding symptoms that occur past 1 year after the surgery.

2. STUDY COLLABORATORS

2.1 CONTRIBUTING INSTITUTIONS & ROLES

Contributing Institutions	*Team Member* *(name and title)*	*Contributing Role* *(i.e., PI, Data Scientist, Manager, etc.)*
Vanderbilt University Medical Center	Michael Matheny (Lead)	*PI* *Network Collaborator* *Real-World Data Source (EHR and peri-op implant registry), Data Analysis,* *Study Design, Study Oversight*
Lahey	*Kimberly Christ (Lead)*	*Network Collaborator* *Real-World Data Source (EHR and peri-op implant registry), Data Analysis,* *Study Design*
Mayo Clinic	Nilay Shah (Lead)	*Network Collaborator* *Real-World Data Source (EHR and peri-op implant registry), Data Analysis,* *Study Design*
Weill-Cornell	*Art Sedrakyan (Lead)*	*Network Collaborator*

		Real-World Data Source (EHR and peri-op implant registry), Data Analysis, Study Design
Yale New Haven Health System	*Joseph Ross (Lead)*	*Network Collaborator Real-World Data Source (EHR and peri-op implant registry), Data Analysis, Study Design*
FDA	*Aron Yustein (Lead)*	*Organizational Sponsor Study Design, Study Oversight*

2.2 CLINICAL EXPERTS

Contributing Institutions	*Team Member* *(name and title)*	*Contributing Role* *(i.e., PI, Data Scientist, Manager, etc.)*
Vanderbilt University Medical Center	*W. Stuart Reynolds, MD, MPH*	*Urologist, Uro-Gyn Surgical Specialist*
Lahey	*Arthur Mourtzinos,MD*	*Urologist, specialist in male and female incontinence and pelvic floor disorders*
Mayo Clinic	*Emanuel Trabuco, MD*	*Specialist in Uro-Gyn and female pelvic floor disorders.*
Weill-Cornell	*Bilal Chughtai, MD*	*Urologist, specialist in male and female incontinence and pelvic floor disorders*

3. STUDY OBJECTIVES

There remains uncertainty with regards to longer term outcomes among women receiving mesh slings for stress urinary incontinence, and this project seeks to address knowledge gaps for long term outcomes among mesh implantations by leveraging electronic health record data across 5 participating health systems.

Specific Aims: This project seeks to provide a proof of concept for post-market medical device surveillance by assessing the capacity of routinely collected electronic health record data to evaluate the long-term adverse outcomes related to synthetic surgical mesh implantation for stress urinary incontinence.

In pursuit of this goal, this project will:

1) Assess data element availability among key covariates and exposures among patients undergoing surgery for stress urinary incontinence,
2) If data are available, to assess rates of outcomes of mesh erosion, re-operation for SUI, re-operation for mesh revision or removal, chronic pain either as a new or worsening pain or requiring re-operation and voiding symptoms either as a new symptom or requiring re-operation, each with extended surveillance windows after surgery.
3) Specifically, this project will evaluate mid-term (>1 year) and long-term (>2 years) adverse events following synthetic surgical mesh implantation (mid-urethral slings) for female SUI.
4) Lastly, if the data quality and volume are sufficient, we will develop a risk prediction model for the risk of the each of the outcomes stated above among patients receiving mesh for SUI.

In summary, this project seeks to better understand the safety of mesh used for stress urinary incontinence by leveraging electronic health record data. The FDA intends on incorporating these data into its growing portfolio of evidence in order to help support regulatory decision making on level of risk

for these procedures and recommendations around use of mesh for this indication. This study has the potential to increase medical knowledge regarding these devices.

4. STUDY DESIGN

This project will be a multi-site retrospective cohort analysis of trans-vaginally placed synthetic mid-urethral slings (MUS) implanted in patients for the indication of stress urinary incontinence for mid- and long-term outcomes (1 year and greater). We will identify all patients at each of the sites that have received a MUS through administrative and device implantation data. The key exposures will be MUS devices identified by administrative codes. Because ascertainment of the surgical approach is critical to the evaluation of post-operative complications, and has differing rates depending on the approach, we will determine which approach was used: Retropubic MUS (RPMUS), Transobturator MUS (TOMUS), Single-Incision Sling (SIMUS), or Adjustable Sling (AMUS). In prior work at Mayo, determination of the surgical approach was present in 100% of cases in the operative notes. We will also identify all patients that received a surgery for SUI without mesh (autologous or cadaveric fascial sling or burch colposuspension or bulking agents) and evaluate the same outcomes of interest in that population separately to provide an indirect comparison group. No direct comparison of mesh and non-mesh groups will be conducted. Patients with concomitant surgeries at the time of trans-vaginal mesh implantation for SUI will be included. The primary outcomes of interest are long-term safety outcomes relevant to these devices and defined in Section 7. In addition, using the Mayo Clinic data, we will be able to validate the electronic data with the manually curated data from 2010-2012[2]. We will leverage this data to better understand how much of the data can be electronically generated and where additional information would need to be collected in an electronic environment.

Beyond the variables collected for exposures, outcomes, and cohort inclusion/exclusion, important covariates relevant to the device exposures and outcomes, and present prior to the surgery, will also be collected.

These include:

- Patient demographics
- Chronic pain
- Prior abdominal surgery
- Receipt of urodynamic testing (structured data will not have the results)
- BMI
- Insurance payer
- Chronic clinical conditions will be aggregated using the Healthcare Cost and Utilization Project's Clinical Classification Software, which reduces all ICD-9/10 codes to 285 clinically meaningful groups[42]. The CCS has been updated to include ICD-10, which is important, as this project will span ICD-9 and 10 eras.
- Medication exposures will be aggregated using the PCORNet[43] instantiation of the RxNorm controlled vocabulary[44] and leveraging this vocabulary to the Anatomical Therapeutic Chemical (ATC) Level 4 groupings, which are clinically relevant drug classes.

Some co-variates may not be ascertainable in some participating sites' PCORNet CDM instances, and this will be explored and reported. Each of the outcomes, exposures, and covariates will be analyzed for counts in each site and a summarization and report will be provided to characterize the data at each site. Stratified reporting of those receiving surgery for SUI with mesh and those without mesh will be performed.

Next, if the characterization of the data is sufficient for the task, we will pursue a Cox proportional hazards model analysis, with each of the outcomes assessed from the time of the surgery as a time-to-event. We will censor the time-to-event analysis with death or loss to follow-up, defined as a time period

>2 years from last applicable encounter of primary care, Obstetrics & Gynecology, or Urology. The models will be executed at each institutional separately using LASSO Cox to determine the consistently included covariates in each institution[45]. We will then use the final variable list and utilize the method described by Lu and colleagues that uses a distributed analysis approach to obtain an exact model solution without sharing case level data (only intermediate and aggregate model coefficients and matrices)[46].

Because bootstrapping combined with the distributed analysis method would be computationally intensive, we will utilize 10-fold cross validation across all sites for internal validation of the risk model. We assessed overall discrimination using Harrell's concordance statistic (C-statistic)[47]. To provide calibration assessments, we will also evaluate the model at fixed time points of 1 year and 2 year for each outcome using the AUC and the Estimated Calibration Index (ECI)[48]. The ECI looks at the squared difference between the predicted probability and an estimated observed probability, ranging between 0 and 100, with 0 meaning perfect calibration. Additionally, we will graphically analyze calibration by investigating the smoothed observed-to-predicted probability plot[48].

5. TARGET POPULATION

Inclusion criteria:

- All women aged 18 or greater undergoing transvaginal surgery for stress urinary incontinence (index surgery) with or without mesh implantation
- EHR-Based study date range 2010-2019
- Inpatient or outpatient visit

Exclusion criteria:

- No primary care, ob/gyn, or urology visits in the year prior to the surgery
- Prior pelvic organ prolapse surgery
- Prior stress urinary incontinence surgery
- Prior surgery diagnosis of a urethral diverticulum ICD-9-CM code 619.0 or any urinary-genital tract fistula (codes 599.1 and 599.2) in the 90 days prior to the index surgery.

6. STUDY PROCEDURES

We will access the routinely collected observational data from electronic health records at Vanderbilt University Medical Center, Lahey Hospital & Medical Center, Mayo Clinic, Weill-Cornell, and Yale New Haven Health System for this study. For the routine EHR data sources, the valid dates will be from 2010 to the most recently available data. There are no patient recruitment or retention barriers in this project as all data are observational cohort data. There are significant issues around data ascertainment bias that will be addressed in more detail in Study Design & Methods. Patient level data will not leave each institution, only aggregate data or distributed regression analyses, which will remove the requirement for a data sharing agreement and streamline the execution of the project. We will leverage each site's PCORNet common data model and the VUMC site will build the code to transform the data from the PCORNet common data model to the flat analytic file necessary for statistical work.

This project will be a multi-site retrospective cohort analysis of trans-vaginally placed synthetic mid-urethral slings (MUS) implanted in patients for the indication of stress urinary incontinence for mid- and long-term outcomes (1 year and greater). The key exposures will be MUS devices identified by administrative codes and identifying all patients at each of the sites through administrative and device implantation data. Surgical approaches (Retropubic MUS, Transobturator MUS, Single-Incision Sling, and Adjustable Sling) will be determined through natural language processing of operative notes. We will also identify all patients that received a surgery for SUI without mesh (autologous fascial sling or burch colposuspension). The primary outcomes of interest are long-term safety outcomes relevant to these devices and defined in Section 7. In addition, using the Mayo Clinic data, we will be able to validate the

electronic data with the manually curated data from 2010-2012. Each site will also conduct manual chart review of 50 to 100 patient cases for a critical sub-set of covariates, exposures, and outcomes that the research group deems are important, in order to validate the EHR-derived data elements, and assess potential bias among those not compared with chart review. We will leverage this data to better understand how much of the data can be electronically generated and where additional information would need to be collected in an electronic environment.

Beyond the variables collected for exposures, outcomes, and cohort inclusion/exclusion, important covariates relevant to the device exposures and outcomes, and present prior to the surgery, will also be collected. These include patient demographics, chronic pain, prior abdominal surgery, receipt of urodynamic testing (structured data will not have the results), BMI, and insurance payer. In addition, chronic clinical conditions will be aggregated using the Healthcare Cost and Utilization Project's Clinical Classification Software, which reduces all ICD-9/10 codes to 285 clinically meaningful groups[42]. The CCS has been updated to include ICD-10, which is important, as this project will span ICD-9 and 10 eras. Medication exposures will be aggregated using the PCORNet instantiation of the RxNorm controlled vocabulary and leveraging this vocabulary to the Anatomical Therapeutic Chemical (ATC) Level 4 groupings, which are clinically relevant drug classes. Some co-variates may not be ascertainable in some participating sites' PCORNet CDM instances, and this will be explored and reported. Each of the outcomes, exposures, and covariates will be analyzed for counts in each site and a summarization and report will be provided to characterize the data at each site. Stratified reporting of those receiving surgery for SUI with mesh and those without mesh will be performed.

In order to determine the surgical approach, we will supplement the CDM structured data with information from pre-operative planning and operative notes, as described in more detail in Data Collection. In order to extract the information from the text notes, we will first pursue a straightforward string matching approach to extracting the surgical approach, which will include pre-populating the matching algorithm with the standard names of the surgical approaches and common abbreviations, and then iteratively adding terms and variations that are found in the document set for the initial Vanderbilt training corpus. Although this is not a full NLP solution, it is likely that this will be successful primarily because use of surgical approach is not likely to be negated ('we did ***not*** use XX approach but did use YY approach) in the immediate peri-operative reports because they are focused on a narrative of what was done. Also, the possible space of variation in how the terms are represented is not likely to be extreme given the focused nature of the need for extraction. Lastly, deployment of this type of algorithm at each of the sites is straightforward and not as complicated to ensure that it is executed and working as a full NLP solution. We also will attempt to determine the status of hand-cut slings and tensioned slings as part of the approach and surgical plan in the operative note.

Next, if the characterization of the data is sufficient for the task, we will pursue a Cox proportional hazards model analysis, with each of the outcomes assessed from the time of the surgery as a time-to-event. We will censor the time-to-event analysis with death or loss to follow-up, defined as a time period >2 years from last applicable encounter of primary care, Obstetrics & Gynecology, or Urology. The models will be executed at each institutional separately using LASSO Cox to determine the consistently included covariates in each institution[45]. We will then use the final variable list and utilize the method described by Lu and colleagues that uses a distributed analysis approach to obtain an exact model solution without sharing case level data (only intermediate and aggregate model coefficients and matrices)[46].

Because bootstrapping combined with the distributed analysis method would be computationally intensive, we will utilize 10-fold cross validation across all sites for internal validation of the risk model. We assessed overall discrimination using Harrell's concordance statistic (C-statistic)[47]. To provide calibration assessments, we will also evaluate the model at fixed time points of 1 year and 2 year for each outcome using the AUC and the Estimated Calibration Index (ECI)[48]. The ECI looks at the squared difference between the predicted probability and an estimated observed probability, ranging between 0

and 100, with 0 meaning perfect calibration. Additionally, we will graphically analyze calibration by investigating the smoothed observed-to-predicted probability plot[48].

Lastly, we will have access to a manually collected and curated 3,472 patient case series at Mayo Clinic from 2002 to 2012 of patients that underwent surgery for incontinence[2]. See prior publications for more details on that existing data set[2]. We will leverage this existing case series as a validation data set to evaluate the data capture and validity of building the data set from electronic health record sources, and determine overall data fidelity, to be reported to NEST. In more detail, since we are including patients from 2010 onward at Mayo in the EHR-based analysis, we will compare transformed variable from the EHR-based analysis with those in the manually curated registry where they are comparable to assess data quality of the EHR-based data transformation process. Each site will also conduct manual chart review of 50 to 100 patient cases for a critical sub-set of covariates, exposures, and outcomes that the research group deems are important, in order to validate the EHR-derived data elements, and assess potential bias among those not compared with chart review.

6.1 STUDY DURATION AND TIMELINE

Anticipated Start Date 2/17/2020

Requested End Date 03/15/2021

6.2 PROTOCOL DEVIATION HANDLING

There is no data safety monitor board/committee. The PI and study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. The procedures by which collected data will be verified should be provided (i.e., list procedures for verification of secondary endpoint data against original source). It is anticipated that data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report or the IRB Continuing Review, unless the information affects the risk/ benefit profile of the study. In the event of a protocol deviation, the event will be reviewed and reported to the IRB as soon as they occur (or no later than five days after the event is identified)

7. STUDY OUTCOMES

The primary outcomes of interest are:

- Re-operation (revision, incision, excision, removal) or mesh removal
- Chronic pain, defined as pain persisting at least three months after surgery[49]
- Voiding symptoms, defined as recurrence of incontinence or new retention.

All outcomes are determined in the surveillance period after surgery. Re-operation or mesh removal is defined as a surgery for any kind of mid-urethral sling, urethral bulking agent, bladder neck pubovaginal sling (autologous or allograft), or revision for mesh exposure. Resumption of voiding symptoms was defined as subsequent urinary retention, urinary incontinence, and sling revision for urinary retention. Chronic pain is defined as a new post-operative pain score >3 of 10 on vital sign data occurring over at least 3 months or greater of duration, or diagnosis codes related to abdominal and pelvic pain.

8. DATA QUALITY

We will access the routinely collected observational data from electronic health records at Vanderbilt University Medical Center, Lahey Hospital & Medical Center, Mayo Clinic, Weill-Cornell, and Yale New

Haven Health System for this study. In addition, we will have access to a manually collected and curated 3,472 patient case series at Mayo Clinic from 2002 to 2012 of patients that underwent surgery for incontinence, which will be used exclusively to validate the data quality of the electronic health record data extraction and transformation process for the overlapping time period (2002-2012). For the routine EHR data sources, the valid dates will be from 2010 to the most recently available data.

8.1 DATA COLLECTION AND MANAGEMENT

As shown in Figure 1, we will access the data in each institution through the PCORNet or OMOP common data models, which are a normalized sub-set of EHR data that allows standardization of data representation and analytic processes. All sites but Lahey have PCORNet instituted through participation in PCORNet, and Lahey has OMOP. There is a publicly available transform from OMOP to PCORNet that will be utilized to harmonize Lahey to PCORNet. The data available across all sites is limited to patient demographics, inpatient and outpatient administrative condition and procedure codes (ICD-9/10, ICD-9/10 Procedure, CPT, HCPCS, SNOMED-CT), medication orders and/or fills/administrations, laboratory test results, vital signs, and date of death. We prefer prescribing if both are available. The PCORNet common data models in each site except Lahey have undergone extensive data quality assessment through data characterization queries where gaps and systematic miscoding have been reported and addressed over the course of the PCORNet CDRN network lifespan.

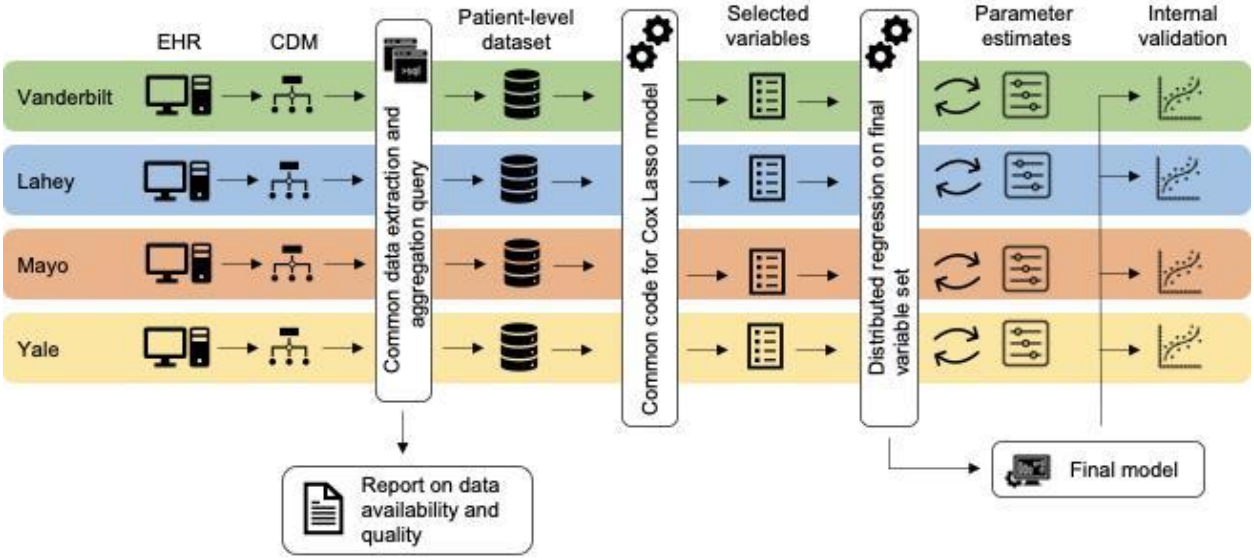

Figure 1: Summary of data collection and data flow process at each site for the variable transformation and distributed regression portions of the project.

Each of the participating sites will supplement their existing CDM-based structured data with free text peri-operative documents for those patient cases that has mesh implantation for stress urinary incontinence, as defined and identified elsewhere. As procedural codes are date specific, all documents +/- 2 days of the administrative code date will be extracted. Notes will then be further filtered to include only 2 notes for each surgical case, the pre-operative planning note (Surgeon, Anesthesia, or Nursing) and the operative note. Sample size estimates are based on a number of referent publications.[50,51] Each site will randomize their patient population and initially select 600 patient documents among 300 patients (2 documents per patient, the primary operative note and a random note from the other notes included) for each surgery. Each site will determine what the surgical approach is at the document level (document assignment) and patient level (merging the 2 document assignments). Vanderbilt will annotate an additional 100 patients to serve as the primary training data set (100 training, 100 internal validation).

There are no patient recruitment or retention barriers in this project as all data are observational cohort data. There are significant issues around data ascertainment bias that will be addressed in more detail in Study Design & Methods. Patient level data will not leave each institution, only aggregate data or distributed regression analyses, which will remove the requirement for a data sharing agreement and streamline the execution of the project.

8.2 MONITORING PLANS

This is an observational study design, and there are no direct interventions for patients, thus a Data and Safety Monitoring Plan is not required, and a Data and Safety Monitoring Board is not required.

9. STATISTICAL ANALYSIS PLAN (SAP)

9.1 STATISTICAL METHODS

Each of the outcomes, exposures, and covariates will be analyzed for counts at each site and a summarization and report will be provided to characterize the data. Stratified reporting of those receiving surgery for SUI with mesh and those without mesh will be performed. While this will allow for indirect comparison of these sub-populations side by side, no direct statistical comparisons between the groups will be made.

Next, if the characterization of the data is sufficient for the task, we will pursue a Cox proportional hazards model analysis, with each of the outcomes assessed from the time of the surgery as a time-to-event. We will censor the time-to-event analysis with death or loss to follow-up, defined as a time period >2 years from last applicable encounter of primary care, Obstetrics & Gynecology, or Urology. The models will be executed at each institutional separately using LASSO Cox to determine the consistently included covariates in each institution[25]. We will then use the final variable list and utilize the method described by Lu and colleagues that uses a distributed analysis approach to obtain an exact model solution without sharing case level data (only intermediate and aggregate model coefficients and matrices)[46].

Because bootstrapping combined with the distributed analysis method would be computationally intensive, we will utilize 10-fold cross validation across all sites for internal validation of the risk model. We will assess overall discrimination using Harrell's concordance statistic (C-statistic)[47]. To provide calibration assessments, we will also evaluate the model at fixed time points of 1 year and 2 year for each outcome using the AUC and the Estimated Calibration Index (ECI)[48]. The ECI looks at the squared difference between the predicted probability and an estimated observed probability, ranging between 0 and 100, with 0 meaning perfect calibration. Additionally, we will graphically analyze calibration by investigating the smoothed observed-to-predicted probability plot[48].

10. STUDY ADMINISTRATION

10.1 CONSENT AND HIPAA AUTHORIZATION REQUIREMENTS

A waiver of consent will be applied for because consent human subjects is not required. There is no patient contact, and the data will be obtained from electronic health records through database queries and search queries are performed according to the project's study procedures defined in this document. Searches are logged and will be audited. De-identified datasets are exported directly from the system into a statistical/analysis program. As no HIPAA identifiers are available in the database, and the proposed project does not plan to re-identify these records, this study meets criteria for non-human subject's research and involves no more than minimal risk and with security measures to protect the privacy and security of the data in place.

There are minimal potential risks to the human subjects. The study proposes to examine electronic medical records of patients. Patients will not be exposed to study materials or protocols; only electronic

medical records will be abstracted retrospectively with the IRB approval in place. Though there is a slight risk of loss of confidentiality or privacy of these subjects, all data will reside within the hospital firewall. The proposed study does not involve any interventions or alternative treatments.

Nonetheless, to ensure confidentiality and appropriate use of the database, all relevant key personnel for this study will enter into a data use agreement, which prohibits any use of the data not described in this protocol, including the re-identification of the database records. Since this study involves no more than minimal risk and with security measures to protect the privacy and security of the data in place noted above, it will not adversely affect the rights and the welfare of the patients in the database.

10.2 RISK/BENEFIT ASSESSMENT

This study is beneficial because it is seeking to better understand the safety of mesh used for stress urinary incontinence (SUI) by leveraging electronic health record data. There remains uncertainty with regards to longer term outcomes among women receiving mesh slings for stress urinary incontinence. For this reason, the FDA has partnered with NEST to conduct a multi -site observational postmarket surveillance of women receiving these devices for SUI, with a particular emphasis on outcomes extending beyond one year. This project phase seeks to address knowledge gaps for mid- and long-term outcomes among mesh implantations by leveraging electronic health record data across 5 participating health systems. The FDA intends on incorporating these data into its growing portfolio of evidence in order to help support regulatory decision making on level of risk for these procedures and recommendations around use of mesh for this indication. This study has the potential to increase medical knowledge regarding these devices.

Aggregated and fully de-identified data will be transmitted back to other participating performance sites so that summary statistics can be calculated for all sites. There are minimal potential risks to the human subjects. The study proposes to examine electronic medical records of patients. Patients will not be exposed to study materials or protocols; only electronic medical records will be abstracted retrospectively with the IRB approval in place. Though there is a slight risk of loss of confidentiality or privacy of these subjects, all data will reside within the hospital firewall. The proposed study does not involve any interventions or alternative treatments.

This study adds little to no additional risk to population of interest. Confidentiality of protected health information (PHI) will be assured by maintaining patient records within the hospital firewall and on an encrypted, secure server used by the hospital information systems for clinical duties. The data will be stored in a secure computing environment, encrypted, and with limited log-in access by study personnel. The same safeguards in place for routine clinical care and PHI will always be maintained for this study. Because we will be working within the electronic medical records, we will not have any data to dispose.

11. RESULTS DISSEMINATION

No case level or individual patient level information will be shared between sites or publicly. All other artifacts of the research study will be shared. This includes study design, data cleaning and transformation code, statistical analysis code, covariate definitions, aggregate data summaries, and final prediction models for each outcome. We will first disseminate the results to the FDA and NEST, and then will follow their guidance for when the materials should be submitted for publication. Should any concerns arise from FDA requiring the information to be released prior to publication for safety reasons, we will involve all sites, the FDA, and NEST in these discussions.

At present, we do not anticipate that we will have device specific information available within the electronic health record data that would allow us to issue specific device safety information, but instead plan on a general analysis by surgical approach and implant type.

Use of Evidence: The FDA has been an important collaborator in the development of this project, as represented by Dr. Aron Yustein, Deputy Director of Clinical Affairs and Chief Medical Office of the FDA

Center for Devices and Radiological Health. As the sponsor of this project, he has provided critical guidance on the particular outcomes, device exposures, and surgical procedures and indications that are of interest to the FDA. There has been an explicit discussion that the evidence generated by this project could impact FDA decision making around the use of synthetic surgical mesh implanted through a trans-vaginal approach for the indication of stress urinary incontinence, and that there is a relative lack of mid and long-term outcome data in these devices for this indication. Dr. Yustein will be an active participant in the research protocol throughout the project and will diffuse the findings to the relevant FDA personnel that would need access to the results. This project does not have any current projected impact on coverage other than through possible indirect effect on future FDA decisions.

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13. APPENDICES

Synthetic Mid-Urethral Slings for Stress Urinary Incontinence in Women
Appendix: Data Collection

Category	Name	Definition, structured?	CDM?	Notes
Covariate	Age @ Procedure	Age as difference between date of surgery and date of birth	Yes- derived to remove PHI	
Outcome	Date of Death	The date on which the patient died.	Yes	Capture as date/time Lahey Comments: Captured only within institution, working on linkage to the SSI Death Index, otherwise would need chart review. Death status is more easily ascertained but not the death of death.
Inc/Excl Criteria	Surgery Indication (POP vs SUI)	Structured Codes Include Sling CPT: 57288 Include Lap sling CPT: 51992	Yes	CPT: 57288 includes retropubic midurethral slings, transobturator slings, and minislings,

				single-incision sling, adjustable sling CPT: 51992 includes laparoscopy approach.
Exposure	Mesh Implantation	Yes/No	Yes	Key Exposure
Covariate	Gender	Gender	Yes	
Covariate	Race	White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander	Yes	
Covariate	Ethnicity	Hispanic or Non-Hispanic	Yes	
Covariate	Women's Health History: pregnancies, vaginal deliveries, and menopausal status [52]	Look for Gravida/Parity in problem list: ex: G3P3? Possible administrative codes: Grand multipara status only (not pregnant) ICD9/10- V61.5/Z64.1 Grand multiparity SNOMED-364325004/452221000000100/ 440681000000102 # Parity LOINC- 11977-6 Unspecified menopausal and post-menopausal disorder ICD 9/10 627.9/N95.9 Premature menopause ICD9/10 256.31/E28.31 Post-menopausal bleeding ICD 9/10 627.1/N95.0	Partial, Admin Codes	May miss portion of data if admin codes only
Outcome	Re-Operation	CPT code based Reoperation for Mesh Revision/Removal sling revision/removal-CPT codes 57287, 10120 Removal of Autologous Tissue Substitute from Urethra, Open Approach (ICD 10 PCS 0TPD07Z). Removal of Synthetic Substitute from Urethra, Open Approach (ICD 10 PCS 0TPD0JZ). Removal of Nonautologous Tissue Substitute from Urethra, Open Approach (ICD 10 PCS 0TPD0KZ). Revision of Autologous Tissue Substitute in Urethra, Open Approach (ICD 10 PCS 0TWD07Z). Revision of Synthetic Substitute in Urethra, Open Approach (ICD 10 PCS 0TWD0JZ). Revision of Nonautologous Tissue Substitute in Urethra, Open Approach (ICD 10 PCS 0TWD0KZ). Reoperation for Mesh Revision/Removal Subtypes: • Hemorrhage/bleeding (ICD9/10 459.0, 998.11, 623.8 or 596.89/ R58, N99.820, N99.821) • Nerve injury (ICD9/10 956.3, 956.5, 956.8, 956.9,957.9/S30-S39, S84.10XA, S74.8X9A) • Pain (ICD9/10 338,338.1,338.2, 338.21, 338.28, 338.29 /R10.2, G89.21, G89.28)	Yes	revision, incision, excision, removal. Represented as a Date, allows time-to-event analysis. Some of the covariate & outcome variables pertaining to degree of recurrence (may not be ascertainable in structured data, will require text search), including urinary urgency as a symptom (depends on the pre-operative visit, under-documented in structured data)

		• Mesh exposure and erosion (ICD9/10 629.31, 629.32/T83.711, T83.721) • Urinary Retention (CPT Code 53500, ICD 9/10 788.20, 788.21/R33.0, • R33.8-R33.9) • Urgency of urination (ICD9/10 788.63/R39.15) • Urge incontinence (ICD9/10 788.31/N39.41) • Bowel injury (ICD9/10 569.83/S36) • Bladder/urethral injury (ICD9/10 596.6,867.0/S37) • Infection (ICD9/10 686.9,998.5,999.3,998.51,998.59/T81) • Retropubic hematoma (ICD 9/10 568.81,,568.81,459.0/K66.1) • • Reoperation for Recurrent SUI: Kaiser ID 59.69, 59.79, 57.89, 70.79 2 Bulking Injection CPT 51715, ICD 9/10 59.72/ PCS 3E0K3GC Laparoscopic Retropubic Urethropexy CPT 51990, 51992, 51999 Abdominal Retropubic Urethropexy CPT 51840,51841 Needle Bladder Neck Suspension CPT 51845 Kelly plication CPT 57220 Cystourethroplasty CPT 51800 Subtypes: • Stress incontinence, female/mixed incontinence (ICD9/10 625.6,788.33/N39.46) • Stress incontinence (female) (male)(ICD10 CM N39.3) S[53]		
Outcome	Mesh Removal	General, • CPT 57287-Removal or revision of sling for stress incontinence (fascia or synthetic) ***some erosions managed surgically may have been coded by a different CPT (i.e. 57295 revise vaginal graft via vaginal approach) and not CPT 57287, which indicates a sling revision/removal. [28]	Yes	Possible Options: (a surgery for any kind of mid-urethral sling, urethral bulking agent, black neck pubovaginal sling (autologous or allograft), or revision for mesh exposure). Represented as a Date, allows time-to-event analysis.
Outcome	Post-Procedural Pain	?, mix of vital sign (pain score >3 of 10 on vital sign data) and likely free text. Also, diagnosis codes related to abd/pelvic pain (if prior pain free).	Some portion	Would have to exclude prior chronic pain or detect specific mention of new pain (free text). Could analyze group with no pre-surgical pain,

				otherwise probably beyond scope. Date/Time of first post-op occurrence. Yale Team: After reviewing the variable list, it seems as if the proposed variables are ascertainable. However, there will be some variables that will be more difficult to capture, for instance, the "post-procedural pain" variable will likely require going through free text and notes to determine if a pain score has been recorded.'
Covariate	Chronic Pain	Admin codes, also possibly pain medication. Chronic suprapubic pain Chronic pelvic, groin, or leg pain- ICD 9/10 625.9, 338.29, 789.09/R10.2, G89.29, R10.30 Chronic postprocedural pain- ICD 9/10 338.28/G89.28 Dyspareunia- ICD 9/10 625.0/N94.10, N94.12, N94.11, N94.19	Med & admin both structured	
Covariate & Outcome	Voiding symptoms: urgency, obstructive symptoms, urinary retention, UTI	Admin codes Urinary Retention ICD9/10 for 596.0, 598.1, 598.2, 598.8, 598.9, 599.6, 599.69, 788.2, 788.21, 788.29, 788.61, 788.62, and 788.65. [28] Urinary Tract Infection (UTI)- >100,000 CFU of bacteria on urine culture and symptoms of UTI Recurrent UTI (≥2 in 6 months or ≥3 in 12 month) Urgency Urinary Incontinence ICD 9/10 (788.31/N39.41) Urinary Retention Requiring Prolonged Catheterization ICD 9/10 788.20/R33.9 and CPT 51701 or 51702 Overactive bladder (OAB)- ICD10 N32.81 or SNOMED 762262008 Urinary Tract Infection ICD 9 599.0 Infection of Kidney, NOS ICD 9 590.9 Urinary Tract Infection, site not specified ICD 10 N39.0 *Urinary incontinence* ICD 9: 625.6 Stress urinary incontinence, female 599.82 Intrinsic sphincter deficiency 788.30 Urinary incontinence, unspecified 788.31 Urge incontinence 788.33 Mixed incontinence (male) (female) 788.34 Incontinence without sensory awareness 788.35 Post-void dribbling		recurrence of incontinence or new retention. subsequent urinary retention, urinary incontinence, and sling revision for urinary retention Capture as date/time SME determined that this may be hard to separate from pre-existing condition

		788.36 Nocturnal enuresis 788.37 Continuous leakage 788.38 Overflow incontinence 788.39 Other urinary incontinence ICD10: N39.3 Stress incontinence (female) (male) N36.42 Intrinsic sphincter deficiency (ISD) R32 Unspecified urinary incontinence N39.41 Urge incontinence N39.46 Mixed incontinence N39.42 Incontinence without sensory awareness N39.43 Post-void dribbling N39.44 Nocturnal enuresis N39.45 Continuous leakage N39.490 Overflow incontinence N39.498 Other specified urinary incontinence *Prolapse* ICD 9: 618.01 Cystocele, midline 618.02 Cystocele, lateral 618.03 Urethrocele 618.81 Incompetence or weakening of pubocervical fascia 618.1 Uterine prolapse without mention of vaginal wall prolapse 618.2 Uterovaginal prolapse, incomplete 618.3 Uterovaginal prolapse, complete 618.4 Uterovaginal prolapse, unspecified 618.5 Prolapse of vaginal vault after hysterectomy 618.6 Vaginal enterocele, congenital or acquired 618.84 Cervical stump prolapse 618.04 Rectocele 618.05 Perineocele 618.82 Incompetence or weakening of rectovaginal fascia 618.00 Unspecified prolapse of vaginal walls 618.09 Other prolapse of the vaginal walls without mention of uterine prolapse 618.7 Old laceration of muscles of pelvic floor 618.83 Pelvic muscle wasting 618.89 Other specified genital prolapse 618.9 Unspecified genital prolapse ICD-10 CM : N81.0 Urethrocele N81.10 Cystocele, unspecified N81.11 Cystocele, midline N81.12 Cystocele, lateral N81.2 Incomplete uterovaginal prolapse N81.3 Complete uterovaginal prolapse N81.4 Uterovaginal prolapse, unspecified N81.5 Vaginal enterocele N81.6 Rectocele N81.89 Other female genital prolapse N99.3 Prolapse of vaginal vault after hysterectomy		
Exposure	SUI with Mesh	Admin Codes CPT 57288	Yes	Capture as date/time

Exposure	SUI without Mesh	Admin Codes CPT/ICD-9-CM/ICD-10-PCS 51715/ 59.72/3E0K3GC, 3E0K4GC Injection of implant into the urethra and/or bladder neck (collagen implant) CPT/ICD-9-CM/ICD-10-PCS 51990, 51992/59.5/0TSD0ZZ, 0TSD4ZZ Laparoscopic urethral suspension, laproscopic sling procedure CPT/ ICD-9-CM/ICD-10-PCS 51841, 51840/ 59.5/0TSD0ZZ, 0TSD4ZZ Anterior vesicourethropexy, or urethropexy (eg, Marshall-Marchetti-Krantz, Burch) CPT/ICD-9-CM/ICD-10-PCS 51845/59.5/0TSD0ZZ, 0TSD4ZZ Abdominovaginal vesical neck suspension CPT /ICD-9-CM/ICD-10-PCS 57220/ 59.3/0TSC0ZZ, 0TSC4ZZ Kelly plication of urethrovesical	Yes	Capture as date/time
Outcome	Mesh Erosion	Admin Codes: ICD-9-CM codes for mesh erosion: 996.30, 996.39, 996.59, 996.60, 996.65, 996.69, 996.70, 996.76, 996.79, 939.0, 939.2, and 939.9 ICD 10 CM: T83.498A, T85.698A, T85.79XA, T83.598A, T85.79XA, T85.9XXA, T83.89XA, T85.898A, T19.0XXA, T19.2XXA, T19.9XXA Surgical Complications: ICD 9/10 629.31/T83.711 Erosion of implanted vaginal mesh ICD 9/10 629.32/T83.721S Exposure of implanted vaginal mesh ICD 9/10 996.76/T83.9 Complication of genitourinary device, implant or graft ICD9/10-PCS V58.2/30233N1, 30233P1, 30233H1 Blood transfusion ICD9/10 998.5/ T81.49XA, T81.40XS, T81.41, T81.43, T83.5, T83.6 Postoperative infection ICD 9/10 778.2/R33.9 Urinary retention		Capture as date/time Exclude 629.3-complication of implanted vaginal mesh and other prosthetic materials, 629.31-erosion of implanted vaginal mesh, or 629.32-exposure of implanted vaginal mesh because these ICD-9 were not released until 2011? [28] SME determined that topical estrogen could be prescribed for other reasons
Outcome	Urethral fistula	Admin Codes ICD 9- 599.1 ICD 10-N36.0	Yes	Capture as date/time
Covariate	Prior Abdominal Surgery Or Pelvic Radiation Therapy	Admin Codes: Personal history of irradiation-V15.3/Z92.3, Irradiation cystitis- N30.4 CPT/ICD 9/ICD 10 for prior abdominal surgery:	Yes	Yes/No

		Hysterectomy: 00846, 00855, 00944, 01962, 01963, 01969,45126, 51597, 51925, 56308, 58150, 58152, 58180, 58200, 58205, 58210, 58240, 58260, 58262, 58263, 58265, 58267, 58270, 58275, 58280, 58285, 58290, 58291, 58292, 58293, 58294, 58541, 58542, 58543, 58544, 58548, 58550, 58552, 58553, 58554, 58570, 58571, 58572, 58573, 58575, 58951, 58953, 58954, 59135, 59525, 59560, 59561, 59580, 59581 /68.9/Z90.711 Cesarean section: 00850, 59500, 59501, 59520, 59521, 59540, 59541/649.81/O75.82 Appendectomy: 44950, 44955, 44960, 44970, 49315, 56315/V45.79/Z90.89 Hernia repair: 49505, 49507, 49520, 49521, 49525, 49550, 49553, 49555, 49557, 49560, 49561, 49565, 49566, 49570, 49572, 49585, 49587, 49590, 49650, 49651, 49652, 49653, 49654, 49655, 49656, 49657, 49659/53.5/0WQF0ZZ, 0WQF3ZZ, 0WQF4ZZ Cholecystectomy: 47562, 47563, 47564, 47600, 47605, 47610, 47612, 47620/51.0-51.04/0FT40ZZ Colectomy: 44139, 44140, 44204, 44205, 44206, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44157, 44158, 44160,44320, 44322, 44799, 45110, 45111, 45112, 45113, 45114, 45119, 45120, 45121, 45123, 44204, 44205, 44206, 442Ø7, 442Ø8, 4421Ø, 44211, 44212, 44213, 44238, 45395, 45397/45.8, 45.81, 45.82, 45.83/0DTE4ZZ, 0DTE0ZZ, 0DTE7ZZ, 0DTE8ZZ Lysis of abdominal adhesions: 44108, 44005, 58660, 58740, 53500/ 54.5, 54.51, 54.59/0DN84ZZ, 0DNE4ZZ, 0DNJ4ZZ, 0DNU4ZZ, 0DNV4ZZ, 0DNW4ZZ, 0FN04ZZ, 0FN44ZZ, 0FN48ZZ 0FN54ZZ, 0FN64ZZ, 0FN74ZZ, 0FN84ZZ, 0FN94ZZ, 0FNG8ZZ Oophorectomy- 58661, 49321-51, 58940/V45.77/ Z90.722, Z90.721 Cystocele and rectocele repair- 57260-51, 57282, 57267, 57270, 61809, 57240/70.50/ 0JQC0ZZ, 0JQC3ZZ		

		Gastrectomy- 43631, 43632, 43633, 43634/V45.75/Z90.3 Hysterectomy[54], abdominal and vaginal C section Appendectomy Hernia repair Cholecystectomy Colectomy or colorectal resection Excision, lysis peritoneal adhesions Oophorectomy, unilateral and bilateral Repair of cystocele and rectocele, obliteration of vaginal vault Gastrectomy Other		
Outcome	Surgical Site Infection	Admin Codes & Free Text Pelvic, perineal abscess, or infection due to internal prosthetic device, implant and graft Infection due to implant: 996.69/T85.79XA Pelvic abscess ICD9/10:567.22/K65.1 614.3/N73.0 614.9 or 616.9/N73.9 614.4/N73.1 614.5/N73.5, N73.3 Perineal abscess ICD9/10: 682.2/L02.215	Partially	Capture as date/time Lahey Question: Can antibiotic use in within X days be a proxy for SSI?
Outcome	Organ Mesh Perforation (vagina, urinary tract)	Admin Codes & Free Text (Possibly) • Erosion of other implanted mesh to organ or tissue ICD10CM-T83.712 • Erosion of implanted urethral mesh to surrounding organ or tissue, initial encounter-T83.712A • Erosion of implanted urethral mesh to surrounding organ or tissue subsequent encounter-T83.712D • Erosion of implanted urethral mesh to surrounding organ or tissue, sequela-T83.712S • Exposure of implanted urethral mesh into urethra ICD10- T83.722 • Exposure of implanted urethral mesh into urethra, initial encounter T83.722A • Exposure of implanted urethral mesh into urethra, subsequent encounter-T83.722D • Exposure of implanted urethral mesh into urethra, sequela- T83.722S	Yes	Direct surgical complication, capture as date time
Exposure	Pelvic Organ Prolapse (POP) repair surgery plus Mesh Urinary Sling (MUS).	CPT: • Cystocele/rectocele repair – 57260 • Anterior colporrhaphy, repair of cystocele with or without repair of urethrocele -57240 • Repair of enterocele, vaginal approach (separate procedure) -57268 ICD-10 CM :		

		• Urethrocele N81.0 • Cystocele, unspecified N81.10 • Cystocele, midline N81.11 • Cystocele, lateral N81.12 • Incomplete uterovaginal prolapse N81.2 • Complete uterovaginal prolapse N81.3 • Uterovaginal prolapse, unspecified N81.4 • Vaginal enterocele N81.5 • Rectocele N81.6 • Other female genital prolapse N81.89 • Prolapse of vaginal vault after hysterectomy N99.3		
Covariate	Body Mass Index (BMI)	Vital Signs	Yes	Directly populated or calculated with height and weight fields. The most recent prior height is used (any prior date), and most recent weight within 365 prior days.
Covariate	Insurance Payer	Administrative data: Payer is the expected primary payer for the hospital stay[54]. To make coding uniform across all HCUP data sources, payer combines detailed categories into general groups: • Medicare: includes patients covered by fee-for-service and managed care Medicare • Medicaid: includes patients covered by fee-for-service and managed care Medicaid • Private Insurance: includes Blue Cross, commercial carriers, and private health maintenance organizations (HMOs) and preferred provider organizations (PPOs) • Uninsured: includes an insurance status of *self-pay* and *no charge* • Other: includes Worker's Compensation, TRICARE/CHAMPUS, CHAMPVA, Title V, and other government programs.	Yes	Primary or secondary payers too (may not be possible)?
Covariate	Urodynamic Testing	Administrative data and Free Text Full urodynamic testing[55] would result in reporting the following four CPT codes: • 51741 for complex uroflowmetry • 51729 for complex cystometrogram, including measurement of urethral pressure and bladder voiding/flow pressure	Yes	The decision previously was to defer collection of this variable due to lack of structured data availability. Could collect whether it was done or not?

		• 51784 or 51785 for the EMG + • 51797 for the abdominal pressure, whether measured rectally or vaginally		

Covariate	Surgical Route	Free Text, Pre-Op Consult & Op Note ***See extensive list at bottom for potential procedure codes used by prior study	Supplemental Proposal to extract this from Free Text was generated	Retro-Pubic (RPMUS) Trans-Obturator (TOR) Single Incision (SIMUS) Adjustable Sling (AMUS)
Covariate	Smoking History	Partial	Partial	This variable may not be able to be used because of a mix of structured and free text representations. Lahey ?: Can active smoking status based on nicotine levels>2 be used as a covariate as it's often performed on preop.
Covariate	OB Tape Type 2/3	Free Text, not structured Sling Brand Names and Manufacturer: [53] • Advantage (Boston Scientific) • Advantage Fit (Boston Scientific) • Aris TOT Tape (Mentor) • Desara TV (Caldera) • GMD Universal (GMD) • Lynx Suprapubic (Boston Scientific) • Miniarc (AMS) • Miniarc Precise (AMS) SIS • Monarc (AMS) • Solyx (Boston Scientific) • Sparc (AMS) • TVT Secur (Gynecare) • Transvaginal Tape-TVT (Gynecare) • Transvaginal Tape-Obturator (TVT-O) (Gynecare) • Obtryx Curved (Boston scientific) • Obtryx Halo (Boston scientific)	No	
Covariates	Clinical Classification Software (CCS)	Yes, admin codes Diabetes mellitus HTN Coronary artery disease Peripheral vascular disease Hyperlipidemia	Yes	Clinical Classification Software (CCS) for ICD-9-CM is a database and software tool that was developed as part of the Healthcare Cost and Utilization (HCUP), a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality. THe CCS was updated to include ICD-10-CM ; Clinical Classifications Software Refined (CCSR). 285 clinically meaningful groups with both ICD9 & ICD10 representations

				SME was ok with broader represent CCS would be sufficient
Covariates	Medication Classes – ATC Level 4 Groupings	Yes, either as orders or medication fills, need clarification per site on availability	Yes?	Level 4 ATC is generally a medication class level grouping. We intend on measuring exposure at the time of surgery, and possibly any exposure in the last 6 months. Yes/No for each variable.

EXAMPLES OF DEFINITIONS OF PROCEDURES AND ICD-9 PROCEDURE CODES

Source: Chughtai B, Barber MD, Mao J, Forde JC, Normand ST, Sedrakyan A. Association Between the Amount of Vaginal Mesh Used with Mesh Erosions and Repeated Surgery After Repairing Pelvic Organ Prolapse and Stress Urinary Incontinence. *JAMA Surg.* 2017;152(3):257–263. doi:10.1001/jamasurg.2016.4200

Mesh-specific ICD-9 procedure codes:

Repair of cystocele and rectocele with graft or prosthesis 70.53
Repair of cystocele with graft or prosthesis 70.54
Repair of rectocele with graft or prosthesis 70.55
Vaginal construction with graft or prosthesis 70.63
Vaginal reconstruction with graft or prosthesis 70.64
Vaginal suspension and fixation with graft or prosthesis 70.78
Other operations on cul-de-sac with graft or prosthesis 70.93
Insertion of biological graft 70.94*
Insertion of synthetic graft or prosthesis 70.95*

Mesh-specific CPT-4 Code:

Insertion of mesh or other prosthesis for repair of pelvic floor defect 57267

General Prolapse Repair codes:

Repair of cystocele and rectocele, no graft 70.50
Repair of cystocele, no graft 70.51
Repair of rectocele, no graft 70.52
Other operations on cul-de-sac (repair of vaginal enterocele), no graft 70.92
Vaginal construction, no graft 70.61
Vaginal reconstruction, no graft 70.62
Vaginal suspension and fixation, no graft 70.77
Colpocleisis 70.80
Other uterine suspension 69.22
Vaginal repair of chronic inversion of uterus 69.23
Other repair of uterus and supporting structures 69.29
Other operation on supporting structure of the uterus 69.98
Obliteration of vaginal vault and total excision of vagina 70.4

General Prolapse CPT-4 Codes:

Rectocele repair 45560
Anterior colporrhaphy, repair of cystocele 57240
Posterior colporrhaphy, repair of rectocele 57250
Combined anteroposterior colporrhaphy with enterocele repair 57265
Combined anteroposterior colporrhaphy 57260

Enterocele Repair—vaginal approach 57268
Enterocele Repair — abdominal approach 57270
Colpocleisis 57120
Colpopexy, vaginal, extraperitoneal approach 57282
Colpopexy, vaginal, intraperitoneal approach 57283
Insertion of mesh; vaginal approach 57267
Pereyra procedure, including anterior colporrhaphy 57289
Removal or revision of sling for SUI 57287
Revision (including removal) of prosthetic vaginal graft; vaginal approach 57295
Sling operation for SUI 57288
Uterine suspension 58400
Uterine suspension 58410
Vaginal hysterectomy, with repair of enterocele 58270
Vaginal hysterectomy, with colpourethrocystopexy, complicated 58293
Vaginal hysterectomy with repair of enterocele, complicated 58294

Sling Codes:
Retropubic Urethral Suspension 59.4, 59.71, 59.79
*Must be used concurrently with other prolapse repair codes.

International Classification of Diseases (ICD)-9/10 Diagnosis and Procedure Codes [56]

Diagnoses

Urinary incontinence	625.6/N39.3 Stress urinary incontinence, female 599.82/N36.42 Intrinsic sphincter deficiency 788.30/R32 Urinary incontinence, unspecified 788.31/N39.41 Urge incontinence 788.32/N39.3 Stress urinary incontinence, male 788.33/N39.46Mixed incontinence (male) (female) 788.34/N39.42 Incontinence without sensory awareness 788.35/N39.43Post-void dribbling 788.36/N39.44 Nocturnal enuresis 788.37/N39.45 Continuous leakage 788.38/N39.490 Overflow incontinence 788.39/N39.4 Other urinary incontinence
Prolapse	618.01/N81.11 Cystocele, midline 618.02/N81.12 Cystocele, lateral 618.03/N81.0 Urethrocele 618.81/N81.82 Incompetence or weakening of pubocervical fascia 618.1 Uterine prolapse without mention of vaginal wall prolapse 618.2/N81.2 Uterovaginal prolapse, incomplete 618.3/N81.3 Uterovaginal prolapse, complete 618.4/N81.4 Uterovaginal prolapse, unspecified 618.5/N99.3 Prolapse of vaginal vault after hysterectomy 618.6/N81.5 Vaginal enterocele, congenital or acquired 618.94/N81.85 Cervical stump prolapse 618.04/N81.6 Rectocele 618.05/N81.81 Perineocele 618.82/N81.83 Incompetence or weakening of rectovaginal fascia 618.00/N81.4Unspecified prolapse of vaginal walls 618.09/N81.89 Other prolapse of the vaginal walls without mention of uterine prolapse

	618.7/N88.1 Old laceration of muscles of pelvic floor 618.83/N81.84 Pelvic muscle wasting 618.89/N81.89 Other specified genital prolapse 618.9/N81.9 Unspecified genital prolapse
Surgical Complications	629.31/T83.711 Erosion of implanted vaginal mesh 629.32/T83.721 Exposure of implanted vaginal mesh 996.76/T83.9 Complication of genitourinary device, implant or graft V58.2 Blood transfusion 998.5 Postoperative infection 778.2/R33.9 Urinary retention

Procedures

SUI Procedures – Sling	59.4/ 0TSC4ZZ Suprapubic sling operation 59.79/ 0TQD3ZZ Pubovaginal sling; Anterior urethropexy; Repair of stress incontinence NOS
SUI Procedures - Burch	59.5/ 0TSD4ZZ, 0TSD0ZZ Retropubic urethral suspension (Burch)
SUI Procedures - Other	59.6/ 0TSC4ZZ, 0TSC0ZZ Paraurethral suspension 59.71/ 0TUC0KZ Levator muscle operation for urethrovesical suspension 59.72/ 3E0K4GC Injection of implant into urethra and/or bladder neck
Anterior Repair	70.51/ 0JQC0ZZ, 0JQC3ZZ Repair of cystocele 70.54/ 0JUC07Z, 0JUC0JZ, 0JUC0KZ, 0JUC37Z, 0JUC3JZ, 0JUC3KZ Repair of cystocele with graft or prosthesis
Posterior Repair	70.52/ 0JQC0ZZ, 0JQC3ZZ Repair of rectocele 70.55 Repair of rectocele with graft or prosthesis 70.53 Repair of cystocele and rectocele with graft or prosthesis
Anterior and Posterior Repair	70.50 Repair of cystocele and rectocele 70.53 Repair of cystocele and rectocele with graft or prosthesis
Apical Repair	69.2/ 0UN48ZZ, 0UQ40ZZ, 0UQ43ZZ, 0UQ44ZZ, 0UQ48ZZ, 0US48ZZ Repair of uterine supporting structures 70.4/0UTG0ZZ, 0UTG4ZZ, 0UTG7ZZ, 0UTG8ZZ Obliteration and total excision of the vagina 70.77 Vaginal suspension 70.78/ 0UUG07Z, 0UUG0JZ, 0UUG0KZ, 0UUG47Z, 0UUG4JZ, 0UUG4KZ, 0UUG77Z, 0UUG7JZ, 0UUG7KZ, 0UUG87Z, 0UUG8JZ, 0UUG8KZ Vaginal suspension and fixation with graft or prosthesis 70.8/ 0ULG7DZ, 0ULG7ZZ, 0ULG8DZ, 0ULG8ZZ, Obliteration of the vaginal vault (LeFort) 70.92/ 0ULF7DZ, 0ULF7ZZ, 0ULF8DZ, 0ULF8ZZ, 0UQF0ZZ, 0UQF3ZZ, 0UQF4ZZ, 0UQF7ZZ, 0UQF8ZZ, 0USF0ZZ, 0USF4ZZ, OUSF8ZZ, 0UTF0ZZ, 0UTF4ZZ, 0UTF7ZZ, 0UTF8ZZ Other operations on cul-de-sac 70.93/ 0UUF07Z, 0UUF0JZ, 0UUF0KZ, 0UUF47Z, 0UUF4JZ, 0UUF4KZ, 0UUF77Z, 0UUF7JZ, 0UUF7KZ, 0UUF87Z, 0UUF8JZ, 0UUF8KZ Other operations on cul-de-sac with graft or prosthesis 70.95 Insertion of synthetic graft or prosthesis
Hysterectomy	68.3/ 0UT90ZL, Subtotal abdominal hysterectomy 68.39 Other and unspecified subtotal abdominal hysterectomy 68.4 Total abdominal hysterectomy 68.49/ 0UT90ZZ, 0UTC0ZZ Other and unspecified total abdominal hysterectomy 68.6/ 0UT44ZZ Radical abdominal hysterectomy

	68.69/ 0UT40ZZ Other and unspecified radical abdominal hysterectomy 68.5 Vaginal hysterectomy 68.59/ 0UT97ZL Other and unspecified vaginal hysterectomy 68.7 Radical vaginal hysterectomy 68.79/ 0UT47ZZ, 0UT48ZZ, 0UT97ZZ, 0UT98ZZ, 0UTC7ZZ, 0UTC8ZZ Other and unspecified radical vaginal hysterectomy 68.31/ 0UT94ZL Laparoscopic supracervical hysterectomy 68.41/ 0UT94ZZ, 0UTC4ZZ Laparoscopic total hysterectomy 68.51/ 0UT9FZL Laparoscopic assisted vaginal hysterectomy 68.61 Laparoscopic radical abdominal hysterectomy 68.71/ 0UT9FZZ Laparoscopic radical vaginal hysterectomy 68.9 Other and unspecified hysterectomy
Vaginal Hysterectomy	68.5 Vaginal hysterectomy 68.51 Laparoscopic assisted vaginal hysterectomy 68.59 Other and unspecified vaginal hysterectomy 68.7 Radical vaginal hysterectomy 68.79 Other and unspecified radical vaginal hysterectomy