Final progress report

Developing Evidence for Safety Surveillance from Device Adverse Event Reports

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Structured Abstract

Purpose
This project aimed to develop an annotation model and apply natural language processing (NLP) to device adverse event reports of reoperations following HS to summarize associated patient- and device-specific complications and additional surgeries following HS. The second objective of the study was to evaluate the impact of regulatory activities by examining the differences in reporting sources and patterns before and after the September 2015 panel discussion.

Scope
Device adverse event reports provide valuable information complementary to observational studies using secondary data sources. Due to the narrative nature of device adverse event reports, research using them is limited. Natural language processing is a powerful method to handle complex narrative data in biomedical research. In addition, the reporting quality or behavior may potentially be affected by earlier regulatory activities.

Methods
We obtained 16,783 reports related to reoperation following HS from the Manufacturer and User Facility Device Experience (MAUDE) database that were submitted between January 2005 and June 2018. We created an annotation model based on which NLP models can be developed. The following elements were extracted from the reports: reporting source, medical confirmation or legal process related to the case, patient events, device events, implantation and reoperation timing, and reoperation procedures. We analyzed the most common reporting source, patient and device events, and type of reoperation using the extracted NLP output. We further performed analysis by reporting date to assess the difference in reporting before and after September 2015, when the FDA convened the panel discussion.

Results
Using a developed annotation model and NLP, we found that most adverse event reports of reoperations after HS reported patient events of pain, menstrual disorder, and bleeding and device events of device dislocation, organ perforation, and device breakage. Among the reports that specified reoperation type, we found that hysterectomy represented the majority. Following the 2015 FDA panel discussion, there was a significant increase in adverse event reports over time, predominantly those submitted by lawyers. Additionally, the time interval between device implantation and reoperation and the time interval between reoperation and report in later reports were longer than those in reports submitted before September 2015.

Key Words
Adverse event report, natural language processing, hysteroscopic sterilization, regulatory activity

Purpose

Concerns over the efficacy and safety of hysteroscopic sterilization (HS) with implant arose when thousands of adverse events were reported to the US Food and Drug Administration (FDA). By the end of 2018, 32,773 medical device reports of adverse events related to HS had been received by the FDA.[1] Our previous studies using administrative data in the US found that the risk of reoperation was significantly higher following HS compared to traditional laparoscopic sterilization (LS).[2,3] These population-level studies were able to provide representative estimates of real-world safety events; nonetheless, they lacked the granularity to understand the nature of device complications that were associated with reoperations following initial HS.

The Manufacturer and User Facility Device Experience (MAUDE) database is a publicly available resource, which houses the medical device reports submitted by mandatory and voluntary reporters to the FDA. [4] Although the database cannot be used to provide population estimates of frequencies and severity of device-related problems, reports submitted by manufacturers and patients often contain detailed and specific description of the nature of device complications. However, due to the narrative structure of reports within the MAUDE database, there has been limited use of it for device-related research.

Recently developed automated approaches, such as natural language processing (NLP), can process free-text structures and extract information efficiently from sources such as medical notes and vaccine safety reports.[5,6] Furthermore, the FDA has undertaken a few steps since the concerns over HS have come under the spotlight.[1] In September 2015, the FDA convened a panel discussion focusing on the safety and effectiveness of hysteroscopic sterilization.

Research aim 1: This project aimed to develop an annotation model and apply NLP to MAUDE reports of reoperations following HS to summarize associated patient- and device-specific complications and additional surgeries following HS. Developed annotation model and NLP methods by this proof-of-concept study can are potentially applicable to other future areas for surveillance of device safety. We also identified the advantage of this method as well as the potential difficulties.

Research aim 2: The second objective of the study was to evaluate the impact of regulatory activities by examining the differences in reporting source and pattern before and after the September 2015 panel discussion.

Scope

Hysteroscopic sterilization with an implant, a less invasive alternative to traditional laparoscopic sterilization, was approved by the FDA in 2002. By 2015, the manufacturer estimated that 750,000 women had received the implant. In our previous study, we found that, every year, approximately 1,500 women in New York State received the device in ambulatory surgical settings,[2] not including those receiving procedures in physicians' offices. Based on this, at least 30,000 women would undergo the implant-based procedure in the US annually.

Hysteroscopic sterilization was shown to be over 99% effective with minimal safety concerns in previous phase III and pivotal studies. [7,8] However, HS has been placed under scrutiny as thousands of women have conveyed concerns over its safety and efficacy. By the end of 2018, the FDA has received 32,773 medical device reports of adverse events related to HS.[1] Risks of the procedure include unintended pregnancy, pain, perforation of the uterus or fallopian tubes, and device migration. Our previous studies found that HS was associated with an increased risk of reoperation compared to LS. [2,3] Studies from the United Kingdom and France found similar results.[9,10]

Clinical trials are often conducted in selected centers and have restrictive patient inclusion criteria. For this reason, research with population-level data, such as claims and administrative databases, are useful in providing real-world estimates of device safety events, such as additional surgeries. However, due to the limitation of administrative data, the nature of complications related to these surgeries cannot be ascertained from studies. Nor is there a clinical registry for sterilization procedures currently in place to provide detailed accounts. Anecdotal case reports tentatively provided answers to this question.[11-15] Nevertheless, case reports have limitations with respect to their scopes and sample sizes.

The MAUDE database is a reporting system mandated by the FDA for postmarket device surveillance. It includes adverse event reports of medical devices related to malfunction, injury, and death, submitted by mandatory (manufacturers, importers, and device user facilities) and voluntary (healthcare professionals, patients, and consumers) reporters. Although reports from the MAUDE database cannot be used to estimate prevalence or incidence of device complications, they provide valuable information complementary to observational studies using secondary data sources.

Due to the narrative nature of reports submitted to the MAUDE database, research using the database is limited. Previous research based on the MAUDE database mostly utilized keyword search for simple summarization[16] or manual review of adverse event reports related to the device in question.[17-21] Keyword search is a simple tool to implement; however, it may lack sensitivity and specificity due to the complexity of language. For example, clarification of no complication might be determined to be an event using a keyword search. Manual review can provide accurate accounts of patients' complaints and device-related events but is only feasible when there is a limited number of reports. Manually reviewing thousands of reports, such as adverse event reports related to HS, can be extremely time and resource consuming and does not represent a sustainable measure in long-term device surveillance.

Natural language processing is a powerful method to handle complex narrative data in biomedical research. The NLP systems have been developed to identify, extract, and encode information from literature and clinical narratives. Previously, it has been applied to electronic health records and health-related internet social networks to extract postoperative complications, investigate adverse events related to vaccines, and facilitate pharmacovigilance.[5,6,22,23] Implementing NLP in device research, mirroring the advancement in drug research, has the potential to enable efficient processing of complex information for device surveillance. Establishing an NLP system to analyze adverse event reports of hysteroscopic sterilization from the MAUDE database will significantly expand the capacity to utilize clinically relevant information in the reports to better understand the safety events related to reoperations after HS.

In addition, the development of such a tool will enable future research in device evaluation using a similar methodology by adapting the proposed system to the designated area.

Apart from summarizing device events and related information, implementing NLP to analyze HS reports submitted to the MAUDE will help to understand other aspects of adverse event reporting, such as the impact of regulatory activities. The FDA has undertaken a few steps since the concerns over HS has come under the spotlight.[1] In September 2015, the FDA convened a panel discussion focusing on the safety and effectiveness of hysteroscopic sterilization. Following the advisory committee meeting, the FDA mandated a box warning and a decision checklist to be included in early 2016. The FDA also required the manufacturer to conduct a post-market surveillance study with a comparison group undergoing laparoscopic sterilization. In October 2016, the FDA further issued the final guidance to improve labeling for HS and similar devices. The manufacturer decided to withdraw the device from the US market in 2018.

Regulators often draw critical information from adverse event reports to help determine significant measures such as device recalls and warnings.[24] High-quality reports provide strong assistance to these decisions. However, the availability of high-quality reports may not be as straightforward. The reporting quality or behavior may potentially be affected by earlier regulatory activities.

The MAUDE database not only contains information on detailed device events, it also records source of reporting (provider, consumer, regulatory authority, literature search, or others), type of report (mandatory or voluntary), whether the report was medically confirmed, whether the report was a delayed one, and whether a legal action was invoked. The evaluation of the impact of regulatory activities on adverse event reporting related to HS can serve as a case study to understand the potential influence of regulators on device safety surveillance. Hindsight from the current case will offer valuable knowledge for future occurrences.

Methods

Overall study design

The proposed study will develop an NLP tool to analyze adverse event reports from the MAUDE database with aims to 1) summarize patient and device complications related to removal and 2) assess the impact of regulatory activities on adverse event reporting.

Data source: The Manufacturer and User Facility Device Experience (MAUDE) database

We obtained 16,783 reports related to reoperation following HS from the MAUDE database that were submitted between January 2005 and June 2018. The MAUDE database houses adverse event reports mandated by the FDA for postmarket device surveillance as well as reports submitted by voluntary reporters.[4] It is a publicly available data source. Mandatory reporters include manufacturers, importers, and device user facilities. Mandatory reporters must submit reports when they become aware of information that reasonably suggests that the device may have contributed to a death or serious injury or has malfunctioned. Voluntary reporters include health care professionals, patients, and consumers. The MAUDE database consists of all voluntary reports since June 1991, distributor reports since 1993, and manufacturer reports since August 1996.

The MAUDE database is useful for the following reasons: 1) Adverse event reports submitted were from real-world evidence. 2) Reports submitted to the MAUDE may contain those that were not reported or published by physicians due to concerns for medico-legal risk or time constraints. [24] 3) Adverse event reports can be submitted from anywhere in the nation, even after relocation to other areas or countries. 4) Data in the MAUDE database are accrued over a long period of time among a large population.

Annotation model and NLP development

MAUDE reports are unstructured and use languages different from daily language. It is thus necessary to create annotation models based on which NLP models can be developed. The annotation and NLP models were developed using an iterative process:

- Manual review of randomly selected reports to design the categories of events and elements to be extracted and testing with preliminary NLP to improve the definition;
- Double annotation exercise to improve and assess inter-annotator agreement;
- Annotation of a larger corpus to determine the feasibility of the established annotation model for NLP and identify areas for improvement;
- Annotation of all training and testing reports to develop the NLP model and assess performance.

Annotations, adjudications, and IAA assessments were performed with Multi-document Annotation Environment. [25] The code used for the NLP was written in Python using the spaCy library. [26]

Annotation model specification

The following elements included in the final annotation model were reporting source, medical confirmation or legal process related to the case, patient events, device events, implantation and reoperation timing, and reoperation procedures. We created a data dictionary that specifies details regarding these categories including possible subtypes and examples. We also established labeling rules based on which annotations were conducted. We used three additional labeling categories as modifiers of events, including device, the location where complications happened, and uncertainty of events.

Inter-annotator agreement

Based on the data dictionary developed, we then practiced double annotation to assess and improve the inter-annotator agreement (IAA). This was achieved in two stages.

- Stage 1: Annotate one report each and discuss results and improve consistency;
- Stage 2: Annotate two sets of reports (10 reports each) and discuss after annotating each set of reports.

IAA was measured using Fleiss-Kappa and Krippendorff's alpha statistics. An IAA above 60% is considered a substantial agreement, and an IAA above 80% is considered an almost perfect agreement.

NLP model development

The NLP model developed was based on the named entity recognition (NER) in spaCy, which find the boundary of entities and classify them into pre-defined categories. For the development of the NLP model, gold standard documents by human annotation must be provided as training samples. The gold standard must contain the category and span of each entity.

Training samples were then applied to the NER model, with a dropout rate of 0.2 at each iteration. To validate the trained NLP model, predicted entities from testing samples were compared with those labeled during the annotation process. We calculated the true positive, false positive, and false negative, which were used to calculate the precision, recall, and F measure.

In the feasibility test, we used 200 training samples and 100 testing samples. The feasibility test showed that the NLP was capable of extracting the designated information from the adverse event reports. Based on the feasibility test, we also decided to heavily sample reports from earlier time periods for training due to the variability in reporting language in those reports. Finally, 700 annotated reports were used as training samples, and 300 reports were used as testing samples to train the NLP model for further analysis. (The model performance will be reported in publications.)

Measures and analysis

Study measures analyzed include the following:

- Reporting source and type: reporting source was extracted from NLP output and reporting type was obtained from the MAUDE database. We examined the proportions of reports submitted from each source and the proportion of reports submitted from multiple sources. These two variables were then combined to analyze the reporting pattern.
- Patient and device events: patient and device events were extracted from NLP output and classified. Patient events were further grouped into overarching groups to be analyzed. We examined the number and proportion of patient and device events based on these categories and events. We then patient and device events and categorized into four distinct categories of the presence of events to be examined: reporting both patient and device events, reporting only patient events, reporting only device events, and no events reported.
- Reoperation procedures: Reoperation procedures were extracted from NLP output. Procedures were then categorized based on hierarchies of invasiveness, with hysterectomy being the most invasive followed by salpingectomy, tubal ligation, and other tubal procedures. Additional categories include reversal procedure, re-implantation, laparoscopy, hysteroscopy, laparotomy, other abdominal and gynecologic procedures, and unspecified removal or abdominal procedures.
- Implantation and reoperation time: Implantation and removal time was extracted from NLP output. Reporting time was directly obtained from records. We then calculated the time intervals from implantation to the first reoperation and from the first reoperation to report.

Comparative analyses were then performed by reporting date to assess the difference in reporting before and after September 2015, when the FDA panel was convened. We examined the differences in reporting source and pattern, proportions of reports that were medically confirmed or involved legal process, presence of patient and device events, reoperations reported, and time from reoperation to reporting between reports from these two time periods. Differences were assessed using chi-squared tests and Student's t-tests. All analyses were performed using SAS 9.3 (Cary, NC).

Results

Principal findings from research aim 1: To develop the annotation model and apply NLP to MAUDE reports of reoperations following HS to summarize associated patient- and device-specific complications and additional surgeries following HS.

We extracted six categories of elements from MAUDE reports using the developed NLP model:

- Source: healthcare provider, consumer/patient, lawyer/attorney, regulatory authority, media/social media, FDA docket website, medical literature, clinical studies/investigators, and others;
- Process involved: medical confirmation and litigation;
- Patient events (overarching groups): abdominal/pelvic/back/genital pain, bleeding, menstrual disorder, sexual issues, pregnancy, allergy to metal, and others (see supplemental information for detailed events);
- Device events: perforation of organs, device dislocation/migration/malposition, embedded device, device breakage/fragment, and device shape alteration;
- Reoperation: hysterectomy, salpingectomy, tubal ligation, and other tubal procedures, reversal procedure, re-implantation, laparoscopy, hysteroscopy, laparotomy, other abdominal and gynecologic procedure, and unspecified removal or abdominal procedures;
- Implantation and reoperation time.

Overall, we found that the number of adverse event reports increased significantly over time. The most pronounced increase was in 2017. The majority of reports examined were reported by lawyers, followed by consumers and providers. Most of the reports submitted by patients were submitted through regulatory authority. Fifteen percent of patient reports were submitted through voluntary reporting.

The most common patient events reported among patients undergoing reoperation was abdominal/pelvic/back/genital pain, followed by menstrual disorder and bleeding. The most common device events reported among patients undergoing reoperation was device dislocation, followed by the perforation of organs and device breakage. Among patients who reported being pregnant and underwent reoperation, more than half reported device complications, with the most frequent being device dislocation. Two-thirds of patients undergoing reoperation reported patient events only. One fourth of patients reported both patient and device events (Figure 1).

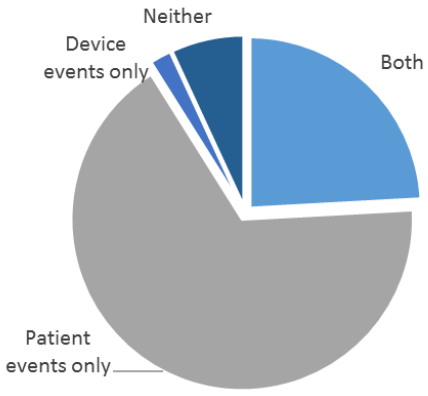

Figure 1. Reporting of patient and device events for reoperation cases

Almost half of the reports did not specify the exact procedure performed for reoperation (either only removal was mentioned, or an unspecified abdominal/pelvic surgery was mentioned). Among the reoperations that were specified, the most common reoperation was hysterectomy, followed by salpingectomy. The mean time from device implantation until the first reoperation was 4 years.

Principal findings from research aim 1: To evaluate the impact of regulatory activities by examining the differences in reporting source and pattern before and after the September 2015 panel discussion.

In the years prior to 2010, all reports were submitted by providers and consumers. In the years leading up to the FDA panel (2011-2015), there were increases in reports submitted by consumers, those submitted through regulatory authority, and those identified from the docket website. After the FDA panel (2016-2018), the vast majority of reports (80%) were submitted by lawyers. With the increase in reports submitted by lawyers, the proportion of reports that were medically confirmed decreased significantly (Figure 2). Of those reports submitted by consumers/patients before the FDA panel in 2015, half of them were submitted through voluntary reporting. After the FDA panel, the majority were submitted through regulatory authority. We also found that reports in later years used more standard language and format when compared with reports in earlier years.

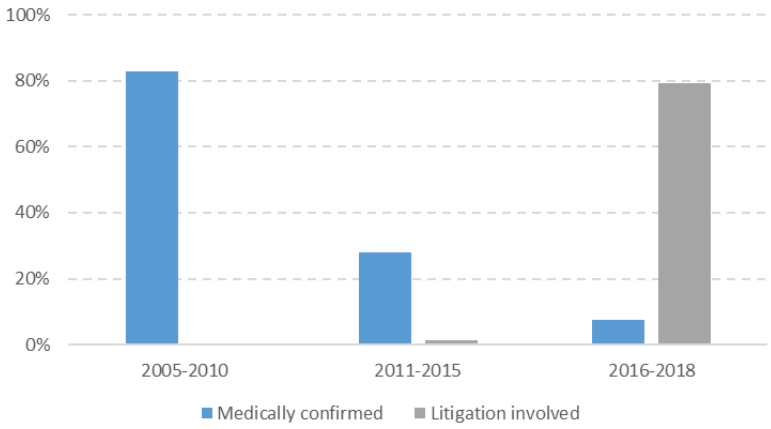

Figure 2. Proportion of cases medically confirmed and involved litigation

After the 2015 FDA panel, a larger proportion of reports of reoperation following HS only reported patient events, compared with those submitted before the panel. Following the FDA panels, more reports submitted did not specify the exact type of reoperations performed. These changes were associated with the presence of a larger proportion of reports submitted by lawyers. Reports submitted lawyers were more likely to report patient events only and were less likely to report the exact reoperation procedure type. On the other hand, a larger proportion of reports submitted by providers reported device events only and were specific about the procedure than others.

The average time between device implantation to the first reoperation was longer for those submitted after the 2015 FDA panel than those submitted before (4 years vs. 2 years). The average interval between reoperation and reporting was also longer for those submitted after the panel (2 years vs. 1 year). The longer interval between reoperation and reporting means that reports submitted after the FDA panel discussion were more likely to be reporting of events that happened years earlier.

Conclusions and implications

Using a developed annotation model and NLP, we found that most adverse event reports of reoperations after HS reported patient events of pain, menstrual disorder, and bleeding and device events of device dislocation, organ perforation, and device breakage. The majority of reports of reoperation only had patient events.

Though case reports tended to report removal cases related to device events,[11-15] these results showed that non-device events may have been the major driver of reoperation following HS. Among the reports that specified reoperation type, we found that hysterectomy represented the majority. In our previous study based on New York State discharge records, we found that, after the initial HS procedure, the risk of undergoing tubal reoperations was higher than that of undergoing hysterectomy.[3] Taken these results together, it can be inferred that those reporting the MAUDE database are more likely to be those who experienced serious events.

The 2015 FDA panel discussion had a few prominent impacts on the adverse event reporting of reoperations. First, there was a significant increase in adverse event reports over time, predominantly those submitted by lawyers. The increase of legal reports not only indicated the effect of the FDA panel discussion on legal activities, it also affected adverse event reporting. One the one hand, more cases are reported, and information regarding events related to reoperation became more abundant, especially patient events. On the other hand, reports submitted by lawyers tended to be less specific about the exact reoperation.

Second, the time interval between device implantation and reoperation and the time interval between reoperation and report in later reports were longer than those in reports submitted before September 2015. It may have been that the FDA panel raised awareness among women, and more reports were being submitted retrospectively.

In summary, our study showed that it is feasible to analyze narrative reports using annotation and NLP models. These methods can be potentially applied to other disease areas and other types of reports. Additionally, our study demonstrated that regulatory activity has a positive effect on stimulating event reporting. However, it may well have unintended consequences on the content of reports.

Supplemental information

Detailed patient event categories:

- Abdominal/pelvic/back pain/genital pain
- Menstrual disorder
- Bleeding
- Sexual problems
- Metal allergy
- Pregnancy
- Abdominal/other gynecologic/urologic: vaginal discharge, abdominal distention, gastrointestinal discomfort, genitourinary infection, other gynecologic complaints, other urologic complaints
- Neurologic: memory change, dizziness, headache/migraine, sensational change, fainting/pass out, balance problems, speech disorder, other neurologic disorder
- Skin/hair/nail: hair change, hive/rash, skin and nail problems
- Head/neck: head and neck problems, eye disorder, oral disorder, otorhinolaryngology disorder
- Joint/bone/muscular: joint/bone/muscular complaints, limb/extremity problems
- Diseases of other systems: cardiovascular complaints, coagulation problems, hormone change, endocrine problems, breast problems, pulmonary disease

- Systemic disease: autoimmune disease, tumor/cancer, other immunologic problems
- Mental/emotional: emotional change, mental problems
- General well-being: fatigue/lack of energy, weight change, sleep disorder, other allergies, taste change, anemia, nutritional deficiency
- Nonspecific events: unspecified infection, nonspecific symptoms (fever, swelling, sweating).

List of Publications and Products

The following manuscripts are being prepared:
1. Manuscript on model developing
Mao J, Sun T, Guiahi M, Chudnoff S, Sedrakyan A, Johnson SB. Developing a model for natural language processing of adverse event reports for the safety evaluation of medical devices. In submission.

2. Manuscript on analytical results
Tentative title: Impact of the FDA regulatory panel on adverse event reporting of reoperations following hysteroscopic sterilization
(This manuscript is at the stage of drafting, which will then undergo critical revision by co-authors. Author list and title are subject to change.)

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