BRIDGING THE PATIENT-CENTER OUTCOME RESEARCH INFRASTRUCTURE AND TECHNOLOGY

INNOVATION THROUGH COORDINATED REGISTRY NETWORKS (CRN)

COMMUNITY OF PRACTICE (COP)

ASPE WEBPAGE: LINK

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EXECUTIVE SUMMARY

Patient-centered outcomes research (PCOR) in devices increasingly relies on data captured at the point of care frequently called real-world data (RWD). The collection of these data can be complex, labor-intensive, and expensive, as it often requires dedicated extensive data collection, validation, and standardization to assure relevancy and reliability of the data. To address these challenges and improve the capacity to evaluate the benefit/risk profile of medical devices in the real- world setting, the U.S. Food and Drug Administration (FDA) Center for Device and Radiological Health (CDRH) launched a series of strategic efforts to advance the national capacity to study medical devices, leading to the establishment of the National Evaluation System for health Technology (NEST). The national system builds on the achievements of clinical registries, that provide foundational value by collecting and maintaining detailed, curated clinical data on millions of patients receiving treatment involving medical device technologies. Registries can provide critical reusable infrastructure that can be used for a variety of analyses related to patient care and outcomes, including benchmarking. The evolution of these registries provides an opportunity for a learning community to address current challenges towards a more sustainable solution and production of RWD.

This report summarizes our achievements in building the Coordinated Registry Network (CRN) Learning Community, a partnership between, FDA/CDRH, and the HHS Office of the Assistant Secretary for Planning and Evaluation, and the national registries (aspiring to become mature CRNs) caring experiences of patients treated by medical device technologies in twelve clinical areas as listed in Table 1. This CRN Learning Community,

Table 1: Coordinated Registry Network (CRN) Learning Community

	CRN Name	Clinical Area
1.	Women's Health Technology Coordinated Registry Network (WHT-CRN)	Women's Health
2.	Vascular Implants Surveillance and Outcomes Network (VISION-CRN)	Vascular
3.	Cardiovascular Devices Coordinated Registry Network (CD-CRN)	Cardiac

4.	Orthopedic Devices Coordinated Registry Network (Ortho-CRN)	Orthopedic
5.	Abdominal Core CRN	Abdominal Hernia
6.	Devices Intended for Acute Ischemic Stroke Intervention (DAISI-CRN)	Acute Ischemic Stroke
7.	National Breast Implants Registry (NBIR)	Breast implants
8.	Study of Prostate Ablation Evidence Development (SPARED-CRN)	Prostate ablation
9.	Robotic Surgery Coordinated Registry Network (Robotic-CRN)	Robotic surgery
10.	Temporomandibular Joint Coordinated Registry Network (TMJ-CRN)	Temporomandibular joint
11.	Venous Access National Guideline & Registry Development Coordinated Registry Network (VANGUARD-CRN)	Venous access
12.	End-Stage Kidney Disease Coordinated Registry Network (ESKD-CRN)	End-stage kidney disease

coordinated by MDEpiNet through Cooperative Agreement with FDA, brought together multiple stakeholders' views and patients' perspectives through harmonization and interoperability, addressing the important unmet needs in the country. Infrastructure development and research was conducted on conditions and treatments that require continued evaluation of safety and effectiveness evidence as it evolves throughout the total product life cycle. Within each of the five objectives during this project, we have achieved the following:

Table 2: Objectives and Accomplishments

Objective	Description	Accomplishments
Objective 1	Advance the CRNs capacity in twelve clinical areas through their development in seven domains of registry maturation.	• Developed multi-stakeholder consensus on CRN maturity Assessment Tool • Created and published a multi-stakeholder CRN Maturity Framework • Facilitated a Self- Assessment of each CRN using CRN Assessment Tool and published report • Advanced the harmonization and capacity to identify minimum core data elements across CRNs • Created implementation roadmaps for participating CRNs • Established the CRN Learning Community and implemented

		multi-stakeholder governance model
Objective 2	Pilot-test and refine the existing device-specific Fast Healthcare Interoperability Resources (FHIR) profiles in an expanded set of CRNs to demonstrate the capture and exchange of CRN data using FHIR.	• Produced FHIR® Implementation Guides
Objective 3	Pilot test and refine the instrument for capturing patient preference information in the End Stage Kidney Disease (ESKD) CRN to evaluate scientifically valid data regarding patient uncertainty in accepting a variety of benefit/risk tradeoffs within a CRN.	• Developed Patient Preference Information (PPI) instrument for End Stage Kidney Disease (ESKD) • Facilitated Development of Minimum Core Data Elements for ESKD CRN • Piloted capture of the PPI in High Performance Integrated Virtual Environment (HIVE)
Objective 4	Advance CRN capacity to produce linked data sets and combine heterogeneous data and developed machine learning techniques for analytics.	• Applied High Performance Integrated Virtual Environment (HIVE) platform as integrated storage and analytical space to support CRNs • Integrated blockchain ledger with HIVE platform to strengthen privacy and traceability • Produced a living catalogue of available data sources/per clinical area a • Validated linkages between registries and claims data • Produced reports of linked data sets for 5 most mature CRNs that can be used for multiple scientific analyses/studies • Developed open access analysis methodologies for machine learning to study causal inference, address missing data and facilitate the linking • Executed linkage studies in most mature CRNs
Objective 5	Develop a gender- and sex-specific outcome measure framework for devices and tested it in the most mature	• Developed gender-specific framework including methodology, lessons learned and outcomes measures.

	CRNs (e.g., in orthopedics, vascular, and abdominal hernia).	• Executed studies to evaluate sex/gender difference in most mature CRNs

Through engagement of key stakeholders, we developed an innovative maturity framework for registries/CRNs using important aspects of infrastructure building. Over a decade of collaborative work culminated into a framework that registries can use as a guideline to help establish or mature their data infrastructure. This was achieved with the help of MDEpiNet collaborators including patient advocacy groups, academicians, clinicians, industry/manufacturers, and regulators. This framework leverages 16 important methodological and infrastructural solutions for the advancement of the CRNs in seven critical domains: unique device identification, patient engagement and patient reported outcomes (PRO), data quality, efficiency, governance, sustainability, and fitness for use during the total product life cycle.

The MDEpiNet Coordinating Center facilitated self-assessment of each CRNs in the seven domains. Such assessment was prioritized to provide an important structural approach to investments in data infrastructure and analytic processes for the advancement of the CRNs, further creating opportunities for harmonization and global collaboration among registries and CRNs to provide reliable and useful real-world data solutions. In individual interviews, CRNs were able to rate their current capacity and achievements as well as identify gaps and challenges in each domain. Mature CRNs as well as early CRNs participated in the assessment and found it immensely beneficial to systematically evaluate their data infrastructure.

Over the course of the project, mature as well as early CRNs have advanced their capacity in the key domain of efficiency in data collection. This was achieved by facilitating the development of core minimum data sets (including definitions for each) for the CRNs listed in using either majority voting or Delphi consensus methods. In collaboration with clinical and informatics experts, patient advocates and industry partners, we identified data across the clinical workflow, including, but not limited to device, anatomic, diagnostics, treatment, pathologic characteristics, and outcomes data elements for each clinical domain to support research and/or surveillance

analysis. Of note, the methodologies were applied to two additional clinical/device areas: Cochlear Implants and Obesity Devices.

Overall, the core minimum data development process permits interoperability across the ecosystem, enhances decision-support systems, enables early detection of adverse event signals, facilitates post-market surveillance, refines decision-making processes with respect to patient/device selection, and facilitates diagnostics and disease management.

Furthermore, to help mature the CRNs in the patient engagement domain, we developed two secure, advanced, and compliant data software solutions: 1) MDEpiNet HIVE and 2) patient-facing mobile applications to capture patient preference information, both which have been used in several CRNs. This allows direct patient decision-making and input in the clinical database. The patient facing apps are also utilized in women's health and orthopedics in pediatric scoliosis for efficient PRO data collection. In addition, this infrastructure has been expanded beyond the basic structured data capture to also include patient preference thresholds based on levels of perceived risk within the end-stage kidney patient population.

Our primary accomplishment was the advancement of the CRN capacity to produce linked data sets and combine heterogeneous data for gathering quality longitudinal and long-term data. We conducted data linkages in Vascular Implants Surveillance and Outcomes Network (VISION), Abdominal Core Health (ACH), and Orthopedic CRNs. In doing so, we established a catalogue of data sources that can be reliably used for conducting device research. We have conducted over 60 investigations using these data sources to showcase their relevance and reliability prior to linking these data sources with various registry data such as the Vascular Quality Initiative, Abdominal Core Health Qualitative Collaborative, and other electronic health records. We conducted over a dozen linkage studies with these data sources using novel methodologies and validated the linkages.

We further utilized the data sources to conduct studies using machine learning methods in women's health and cardiovascular devices. We also developed machine learning methodologies for missing data and causal inferences.

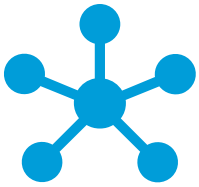
We utilized the most mature CRNs and their data infrastructure to successfully develop a gender- / sex- specific outcome measure framework. Various gender and sex analyses were conducted to compare outcomes in orthopedics, vascular, abdominal hernia devices. The framework for sex- and gender- specific studies was developed based on 1) the studies conducted within the CRNs, 2) the lessons learned from these analyses, and 3) the recommendations of the CDRH Strategic Plan, Health of Women Strategic Plan and CDRH Guidance on the Evaluation of Sex Specific Data on Medical Device Clinical Studies. The framework consists of first identifying between-sex or between-gender differences, followed by the selection of appropriate data sources, the definition and identification of sex and gender in data sources, the development of appropriate statistical analyses, and, finally, the dissemination of findings.

In conclusion, by establishing a CRN maturity framework, assessing the CRN capacity, and then by advancing the CRN infrastructure, we have developed a real-world data and an evidence ecosystem including tools for device research in twelve clinical areas (and expanded it to two additional clinical areas). CRNs are able to adopt a roadmap in each maturity domain for continuous self-improvement and evaluation with the help of the newly established learning community. The CRN learning community will support each CRN to define priorities for the next intellectual and financial investments that they will be making. With continued support from MDEpiNet Coordinating Center there will be opportunities to create more robust real-world data infrastructure and methodologies or build upon existing infrastructure and methodologies. Examples include MDEpiNet HIVE data platform, developing additional patient-facing mobile apps, expanding device libraries, developing distributed and advanced analytics, applying machine learning and artificial intelligence, and developing standardization and harmonization tools for generating real-world evidence critical to regulatory decision-making.

OBJECTIVES

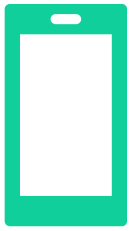
This section is organized by the objectives set to be accomplished during the course of the project. The figure below depicts the top level objectives.

Figure 1: CRN Objectives



1. Advanced the CRNs capacity in twelve clinical areas through their development in seven areas of registry maturation

2. Pilot tested and refined the existing device-specific Fast Healthcare Interoperability Resources (FHIR) profiles in an expanded set of CRNs to demonstrate the capture and exchange of CRN data using FHIR



3. Pilot tested and refined the instrument for capturing patient preferences in End Stage Kidney Disease (ESKD) CRN to evaluate scientifically valid data regarding patient uncertainty in accepting a variety of benefit/risk tradeoffs within a CRN

4. Advanced CRN capacity to produce linked data sets and combine heterogeneous data, and developed machine learning techniques for analytics

5. Developed a gender- and sex- specific outcome measure framework for devices and tested it in the most mature CRNs (e.g., in orthopedics, vascular, abdominal hernia).

OBJECTIVE 1

Advance the CRNs capacity for PCOR use in 12 clinical areas through their development in 7 areas (attributes): (a) patient engagement, (b) unique device identification, (c) data quality, (d) efficiency, (e) governance, (f)

1A – CRN MATURITY FRAMEWORK

CRN assessment tool that will be published on the FDA website, MDEpiNet website and/or a peer- reviewed - journal.

Maturity Framework

For advancing capacity of CRNs, MDEpiNet leadership committee engaged key stakeholders to develop an innovative maturity framework for registries/CRNs using important aspects of infrastructure building. The development process of the framework is described in the recently published manuscript in BMJ-SIT [***See attachment 1 (manuscript with framework)***].[1]

The maturity framework was established under the MDEpiNet and FDA collaborative,[2,3,4] based on the IMDRF guidelines[5], and in collaboration with an expert group of stakeholders from patient advocacy groups, academic, clinical, industry, and regulatory settings. The framework was finalized in 2021 using a modified Delphi consensus method. The framework has important methodological and infrastructural solutions for the advancement of CRNs. Each domain is presented in graduated levels of achievement (levels 1-5) to strategically enhance the CRN infrastructure. The levels are categorized as *Early Learner; Making Progress; Defined Path to Success; Well-Managed; and Optimized*.

[1] Sedrakyan A, Marinac-Dabic D, Campbell B, Aryal S, Baird CE, Goodney P, Cronenwett JL, Beck AW, Paxton EW, Hu J, Brindis R, Baskin K, Cowley T, Levy J, Liebeskind DS, Poulose BK, Rardin CR, Resnic FS, Tcheng J, Fisher B, Viviano C, Devlin V, Sheldon M, Eldrup-Jorgensen J, Berlin JA, Drozda J, Matheny ME, Dhruva SS, Feeney T, Mitchell K, Pappas G. Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000123. doi: 10.1136/bmjsit-2021-000123. PMID: 36393894; PMCID: PMC9660584.
[2] U.S. Food and Drug Administration CDRH. Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps. U.S. Food and Drug Administration (FDA). https://www.fda.gov/media/84409/download. Published 2013. Accessed 07 August 2019
[3] U.S. Food and Drug Administration (FDA) CDRH. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Guidance for Industry and Food and Drug Administration Staff U.S. Food and Drug Administration (FDA). https://www.fda.gov/media/99447/download. Published 2017. Accessed 07 August 2019
[4] The Medical Device Epidemiology Network. http://mdepinet.org. Accessed 29 July 2019.
[5] The International Medical Device Regulators Forum (IMDRF). http://www.imdrf.org/about/about.asp. Accessed 29 July 2019.

1B – CRN ASSESSMENTS

Assessment of each CRN related to each of the attributes along with documentation of the methodology applied and the tailored implementation roadmap to mature along the 7 attributes. Due to sensitivities, this is intended for each CRN to mature and not for comparison of maturity across CRNs.

MDEpiNet Coordinating Center facilitated self-assessment of twelve CRNs utilizing the recently developed CRN maturity framework.[6] The goal with this assessment was to understand the needs and gaps of each CRN possessing the potential to advance in real-world evidence generation using the seven important attributes of registry development. Such assessment was prioritized to provide an important structural approach to investments in data infrastructure and analytic processes for the advancement of the CRNs, further creating opportunities for harmonization and global collaboration among registries and CRNs to provide reliable and useful real-world data solutions. The table below showcases the registry leaders interviewed for the CRN self-assessment:

Table 3: Registry/CRNs interviewed using the maturity framework

	Interviewee	CRN	Date of Interview
1	**Dr. Phil Goodney** **Dartmouth-Hitchcock Medical Center**	VISION CRN	April 1st , 2021
2	**Dr. David Liebeskind, UCLA** **Dr. Sameer Ansari, Northwestern University** **Dr. Adnan Siddiqui, University of Buffalo**	DAISI CRN	April 13th , 2021
3	**Ms. Terrie Cowley** **Temporomandibular Joint Association**	TMJ CRN	April 27th , 2021
4	**Dr. Charles Rardin** **American Urogynecology Society**	UD CRN	April 28th , 2021
5	**Dr. Jeff Levy and Dr. Martin Martino** **Institute of Surgical Excellence**	RASD CRN	May 4th , 2021
6	**Dr. Andrea Pusic, Brigham and Women's Hospital** **Ms. Katie Sommers, Plastic Society Foundation**	NBIR CRN	May 10th , 2021

[6] Sedrakyan A, Marinac-Dabic D, Campbell B, Aryal S, Baird CE, Goodney P, Cronenwett JL, Beck AW, Paxton EW, Hu J, Brindis R, Baskin K, Cowley T, Levy J, Liebeskind DS, Poulose BK, Rardin CR, Resnic FS, Tcheng J, Fisher B, Viviano C, Devlin V, Sheldon M, Eldrup-Jorgensen J, Berlin JA, Drozda J, Matheny ME, Dhruva SS, Feeney T, Mitchell K, Pappas G. Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000123. doi: 10.1136/bmjsit-2021-000123. PMID: 36393894; PMCID: PMC9660584.

7	**Dr. Joseph Bavaria, University of Pennsylvania, Dr. Ralph Brindis, American College of Cardiology, Dr, Vinod Thourani, Piedmont Heart Institute**	Cardiac CRN	May 11th , 2021
8	**Dr. Benjamin Poulose Abdominal Core Health Quality Collaborative**	ACH CRN	June 4th ,2021
9	**Dr. Raj Shah, Dr. Mathew Johnson, Keith Hume Society of Interventional Radiology**	SIR CRN	June 14th , 2021
10	**Ms. Melissa West, American Society of Nephrology/ Kidney Health Initiative Dr. Murray Sheldon, CDRH/FDA**	ESKD CRN	June 15th , 2021
11	**Dr. Liz Paxton, Kaiser Permanente Dr. Art Sedrakyan, Weill Cornell Medicine**	Ortho CRN	Internal correspondence
12	**Dr. Jim Hu and Dr. Art Sedrakyan, Weill Cornell Medicine**	SPARED CRN	Internal correspondence
13	**Dr. Kevin Baskin, Interventional Radiology, VANGUARD**	VANGUARD CRN	Internal correspondence

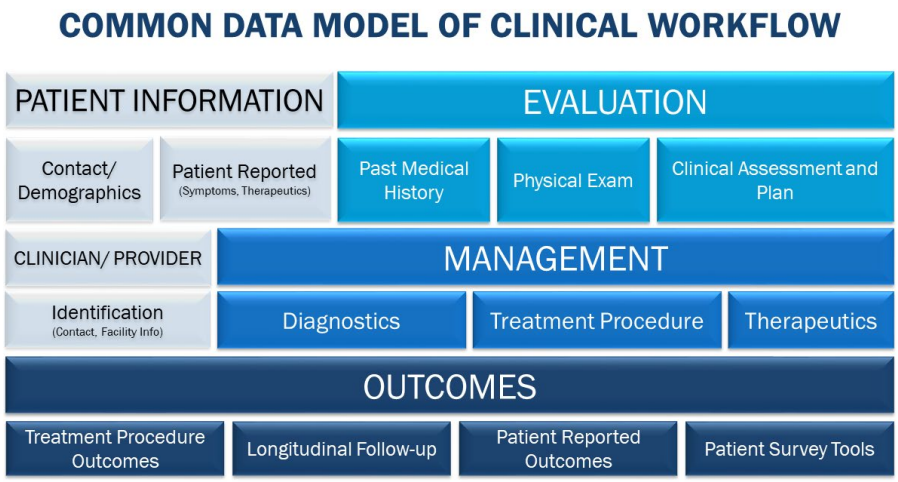
The result of the assessment can be found in the Appendix 2: CRN Assessment Report. Each CRN's current capacity and achievements are highlighted in the assessment, including any major challenges. Each of the CRNs are rated from level 1 to 5 in seven domains of maturity and provided an opportunity and guidance in ways of advancing with specific requirements. Mature CRNs as well as early CRNs participated in the assessment and found it immensely helpful to carefully evaluate their existing real-world data infrastructure. In

"The CRN maturity model helped the Vascular Implant Surveillance and Interventional Outcomes Network (VISION) better understand how expertise in data linkages, data validation efforts, and a strong national registry all contribute towards a mature network. Moreover, the maturity model also helped us to realize that our VISION CRN is ready to make real world data sources an impactful part of post-approval studies for vascular devices, and we look forward to partnerships such as the Long Term EVAR Assessment and Follow-Up System, or LEAF, which will be a CRN-based, multi-society mechanism to better understand long-term performance of endovascular devices used to treat aortic aneurysm"

Philip Goodney, MD, MS

employing this maturity framework, we were careful not to emphasize any requirement of scoring higher or impose any language around mandating domains' maturity for any CRNs to be qualified as effective, useful, or mature. We used caution and sensitivity as the framework is not intended as a system to produce an overall ranking for any CRN, but rather to understand the current capacity in each domain to promote growth. With the help of this maturity framework, we were able to highlight the importance of involving key stakeholders such as patients, professional societies, and manufacturers from the outset.

Figure 2: Clinical Workflow Model



1C – CRN MINIMUM CORE DATA ELEMENTS

A minimum core data set of elements for each CRN (evidence of the attribute "Data Quality"), vetted by the multi-stakeholder community via formal consensus building, including data dictionary and permissible values sets, adherence to international standards and captured by the National Library of Medicine library of common data elements.

The minimum core set of data elements aims to identify the data across the clinical workflow, including, but not limited to device, anatomic, pathologic characteristics, and outcomes data elements for each respective for each clinical domain to support research and/or surveillance analysis.

The goal of identifying the minimum core data set is to support interoperability across the ecosystem, develop/ enhance decision-

support systems, enable early detection of adverse event signals, facilitate post-market surveillance, refine decision-making processes with respect to patient/device selection, diagnosis, and management.

The clinical workflow model as depicted in the Figure 2. has been followed to categorize the data elements within the context of clinical practice.

The minimum core data sets have progressed during the course of this project as follows:

CRN	Consensus or Delphi	Publication Status
WHT-CRN	Delphi	NLM CDE Repository[7]
RAPID	Consensus	Pending Publication
ACHIEv	Consensus	TBD
CATNIP	Consensus	Published[8]
DAISI	Consensus	Published[9]
SPARED	Delphi	Published[10]
Robotics	Consensus	Multiple Publications
TMJ	Delphi	Pending Publication
ESKD	Delphi	TBD
VANGUARD	Consensus/Delphi	Pending Publication

Women's Health Technology Coordinated Registry

The mCDE includes 21 Data Elements and was published in the NLM CDE Repository (link). The data elements were developed by the clinical working group and focused on the women's health-specific

[7] NLM CDE Repository, NLM https://cde.nlm.nih.gov/cde/search?selectedOrg=Women%27s%20CRN; Accessed March 203

[8] Long C, Tcheng JE, Marinac-Dabic D, et al Developing minimum core data structure for the obesity devices Coordinated Registry Network (CRN)BMJ Surgery, Interventions, & Health Technologies 2022;4:e000118. doi: 10.1136/bmjsit-2021-000118

[9] LeRoy H, Gressler LE, Liebeskind DS, Brooks CE, Siddiqui A, Ansari S, Sheldon M, Pena C, Sedrakyan A, Marinac-Dabic D. Developing the foundation for assessment of Devices used for Acute Ischemic Stroke Interventions (DAISI) using a Coordinated Registry Network. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000113. doi: 10.1136/bmjsit-2021-000113. PMID: 36393891; PMCID: PMC9660605.

[10] Golan R, Bernstein A, Sedrakyan A, et al. Development of a Nationally Representative Coordinated Registry Network for Prostate Ablation Technologies. *J Urol*. 2018;199(6):1488-1493.

Network (WHT-CRN)	data elements and related to the following procedures: Total hysterectomy (procedure); Abdominal hysterectomy (procedure); Radical hysterectomy (procedure); Colporrhaphy for repair of enterocele (procedure); Bilateral segmental tubal excision and ligation by endoscopy (procedure); Subtotal abdominal hysterectomy (procedure); Open reversal of female sterilization (procedure); Ligation of fallopian tubes with Fallope ring by endoscopy (procedure); Anorectal myomectomy (procedure); Hysterectomy (procedure); Laparoscopic hysterectomy (procedure); Radiofrequency endometrial ablation (procedure); Vaginal myomectomy (procedure); Repair of vaginal wall prolapse (procedure); Vaginal hysterectomy (procedure); Open myomectomy (procedure); Endometrial ablation (procedure); Total salpingectomy (procedure); Vaginal hysterectomy with total colpectomy and repair of enterocele (procedure); Repair of enterocele (procedure). WHT-CRN mCDE list
Vascular Implants Surveillance and Outcomes Network (VISION-CRN), and RAPID Phase I and Phase 3	The mCDE for peripheral artery disease was implemented in the VQI registry. The additional data elements were developed through a consensus process with clinicians and in collaboration with the informatics experts. Importantly, the existing and new data elements were aligned to the clinical workflow model and additional work is underway to map the clinical concepts to the informatics terminologies and exchange standards that may help feed this data into the registry from electronic health records, and/or capture the data in a structured format to aid in the interoperable objectives of the CRNs. The RAPID working group established the clinical workflow approach that has been leveraged for all mCDE work. In addition, the framework for establishing the clinical, technical and informatics

	metadata was also established by the RAPID/SMART group. These components will be factored into the CRN Data Architecture in future activities. Refer to *Summary and Next Steps* for additional information about the data architecture activities.
Abdominal Core Health International Evaluations (ACHIEv) CRN	Abdominal Core Health International Evaluations (ACHIEv CRN), an international harmonization of abdominal core health/hernia related registries, is underway with plans to deploy DELPHI consensus survey. The goals for data harmonization process are to review variables in each registry, creating variable bridging across registries, and determine the need and scope for DELPHI consensus processes. Since Q1 2021, we've reviewed and analyzed data dictionaries or CRFs from 5 registries from 5 countries (Germany, Sweden, Australia, US, and Denmark) to determine levels of agreement. Using this data, we've begun communications to establish a core minimum data set.
Devices Intended for Acute Ischemic Stroke Intervention (DAISI-CRN)	A multi-stakeholder governance council was convened to identify and achieve agreement on the core minimum dataset. The stakeholders first identified common data elements (CDE) and data collection forms among existing multiple data sources within the clinical space and ensured that identified candidate data elements. Once a quorum was achieved on the identified candidate elements, they were reviewed and included in the minimum CDE with a majority vote/consensus. The final set of data elements included 119 data elements. DAISI mCDEs (Draft)
Study of Prostate Ablation Evidence Development (SPARED-CRN)	The SPARED minimum core data elements aimed to address the evaluation of novel medical devices and drug/device combinations for partial gland ablation. The mCDE was developed by consensus (via Delphi) to capture specific patient demographics, treatment details, oncologic outcomes, functional outcomes, and complications.

Validated health related quality of life questionnaires were selected to capture patient reported outcomes.

SPARED mCDEs

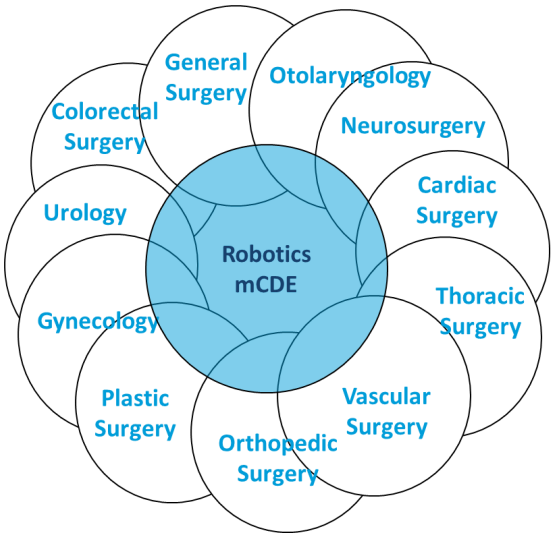
Study of Prostate Ablation Related Energy Devices (SPARED) Collaboration: Patient Selection for Partial Gland Ablation in Men with Localized Prostate Cancer

Development of a Nationally Representative Coordinated Registry Network for Prostate Ablation Technologies. J Urol. 2018;199(6):1488-1493.

Robotic Surgery Coordinated Registry Network (Robotic-CRN)

The Robotics CRN has identified the common robotics surgery data elements by consensus process and serves as the basis for aligning other data element work in the subspecialties. The initial clinical domain for expanding the mCDE is gynecology robotic surgeries as there is substantial work in defining the key data elements for cervical, endometrial, and ovarian cancers. This work has begun and will take into consideration the overlap with the WHT CRN work as well as the subsequent Urogynecological CRN work to ensure consistency across CRNs as much as possible. In the continuation of the work under this grant, each of the subspecialties will be reviewed by clinical experts to determine if there needs to be any additional work and/or further consensus review.

Figure 3: Robotics mCDE Clinical Domains



Temporo-mandibular Joint Coordinated Registry Network

The mCDE for the TMJ CRN was developed using Delphi methodology. The group consensus threshold resulted in the selection of 397 data element, which were aligned to the clinical workflow and further categorized based on progression of the condition for use in the

(TMJ-CRN)

registry. Conditional data elements were identified for patient's undergoing procedures – e.g., total or partial temporomandibular joint replacement – and/or post-procedure outcomes.

The identified mCDE were further defined in the context of technical implementation within HIVE web-application framework. These definitions ensure the validity of data entry process to avoid mistakes, logical consistency, completeness of the forms, and generate visual aids that facilitate data entry by optimizing the appearance and ease of entry through responsive web-design concepts. This variable engineering and form development process, though being separate from the core Delphi processes, required close communication between developers of HIVE web-application platform and Delphi participants. The developers imposed important questions not only about clinical relevance of variables but also the relevance and validity of values that can be recorded for those variables.

The High-performance Integrated Virtual Environment (HIVE) was integrated with an innovative permissioned blockchain platform, to strengthen the provenance of data captured in the registry and drive metadata to record all registry transaction and create a robust consent network. For this technical feasibility project, the engineering team built and implemented several client-side Application Programming Interfaces (API).[11]

TMJ mCDEs (Draft)

[11] Gressler LE, Cowley T, Velezis M, Aryal S, Clare D, Kusiak JW, Cowley A, Sedrakyan A, Marinac-Dabic D, Reardon M, Schmidt, Ginsburg Feldman J, DiFabio V, Bergman S, Simonyan V, Yesha Y, Vasiliu-Feltes I, Durham J, Steen AI, Woods P, Kapos FP, Loyo-Berrios N. Building the Foundation for a Modern Patient-Partnered Infrastructure to Study Temporomandibular Disorders: Infrastructure to Study Temporomandibular Disorders. [Accepted to Frontiers in Digital Health-Health Informatics]

End-Stage Kidney Disease Coordinated Registry Network (ESKD-CRN)	The ESKD CRN has a dedicated objective to begin developing infrastructure for future novel treatments for ESKD. Refer to Objective **3B – Patient-Generated Minimum core data** for more information about the mCDEs.
Registry Development Coordinated Registry Network (VANGUARD-CRN)	To augment the granularity of device data over the device and disease lifespan, an Auxiliary Unique Device Identification (AUDI) Repository of clinically relevant device characteristics is planned as a part of VANGUARD CRN collaborations with core stakeholders. The data elements include the unique device identifier (UDI) components, as well as other device features (such as device type, material, length, etc.), which are not currently standardized among manufacturers and are not included in the Global Unique Device Identification Database (GUDID) but are nonetheless critically relevant to clinical practice and to improvement of patient-focused outcomes. Selection of the data elements and terminology to be included in the AUDI repository will involve - authoritative multi-stakeholder representation through a Delphi process. This process will include stakeholders across the healthcare ecosystem and preparation for the Delphi has been completed.[12]  ***VANGUARD – VACRI mCDEs (Draft)***
Obesity – CATNIP	The Obesity CRN work was done outside of the original scope of this grant, leveraging the MDEpiNet partnerships and networks. iA key first step is to establish a minimum core data structure that provides a common lexicon for endoscopic obesity devices and its

[12] Iorga A, Velezis M, Marinac-Dabic D, Lario RF, Gore B, Bailey C, Gressler LE, Lee RE, Hurst F, Reed T, Mermel LA, Yesha Y, Huff SM. Towbin R, Baskin KM. Venous Access: National Guideline and Registry Development (VANGUARD): Advancing Patient-Centered Venous Access Care Through the Development of a National Coordinated Registry Network. [Accepted to Journal of Medical Internet Research]

corresponding interoperable data elements. Several work groups were subsequently formed to address clinical issues, data quality issues, registry participation, and data sharing.[13]

CATNIP mCDEs (Draft)

Cochlear Implants (Emerging)

Emerging Cochlear Implant (CI) CRN also leveraged the existing PCORTF grant capabilities, although originally outside of the scope of the grant. As cochlear implant technologies advance, new concerns arise such as cochlear implants with capabilities for remote and Artificial Intelligence-based self-programming, expansion of patients' candidacy using real-world evidence (RWE), and the need for consensus on core data elements necessary for the clinical evaluation and research of cochlear implants. The work coincided with the February 2022 FDA- organized workshop so that an initial consensus Delphi survey was completed for the mCDE for cochlear implants centered around the clinical evaluation and research, which will support regulatory decisions making.

The data elements will be organized into the following groups, following the clinical workflow activities for patients who are diagnosed with hearing loss that require cochlear implant procedures.

[13] Long C, Tcheng JE, Marinac-Dabic D, et al. Developing minimum core data structure for the obesity devices Coordinated Registry Network (CRN)BMJ Surgery, Interventions, & Health Technologies 2022;4:e000118. doi: 10.1136/bmjsit-2021-000118

Section I: Patient Information (Demographics, Past Medical History)

Section II: Pre-Implant Candidacy and Post-Implant Outcome Evaluation (Efficacy and Effectiveness)

Section III: Surgical Procedures

Section IV: Post-implant Activation/Programming/Device use

Section V: Post-implant Evaluation ***(Safety)***

stakeholders.

Note: the minimum core data elements are targeted for completion in 2023

1D – IMPLEMENATION ROADMAP

Report, submitted for publication that evaluates how the tailored implementation roadmaps were adopted, including which attributes are easier to adopt and which ones might require resources. Such a report will be written to inform other registries what it takes to adopt the attributes.

MDEpiNet and its partners have developed a CRN assessment tool based on the seven domains of maturity. An expert group of MDEpiNet collaborators from academic, clinical, industry, and regulatory settings participated to develop the framework for CRN maturation.[14] The seven domains of the CRN maturity framework are Device Identification; Patient-reported outcomes and Patient engagement; Data Quality; Efficiency; Governance & Sustainability; Health Care Quality Improvement; and Total Product Life Cycle. Each CRN will be able to use this tool to self-assess their maturity.

The CRNs are in the process of implementing tailored roadmaps related to each attribute of the maturity framework that helps them advance their infrastructure. The

[14] Sedrakyan A, Marinac-Dabic D, Campbell B, Aryal S, Baird CE, Goodney P, Cronenwett JL, Beck AW, Paxton EW, Hu J, Brindis R, Baskin K, Cowley T, Levy J, Liebeskind DS, Poulose BK, Rardin CR, Resnic FS, Tcheng J, Fisher B, Viviano C, Devlin V, Sheldon M, Eldrup-Jorgensen J, Berlin JA, Drozda J, Matheny ME, Dhruva SS, Feeney T, Mitchell K, Pappas G. Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000123. doi: 10.1136/bmjsit-2021-000123. PMID: 36393894; PMCID: PMC9660584

implementation involves solutions in each of the seven domains to strategize on future investments. As part of this effort, we continued working with each CRN to define priorities for the next intellectual and financial investment that they will be making.

The following solutions/tools can be applied by CRNs that best fit their need in a particular domain and are strategically important for them.

Clinically Meaningful Device Attributes

Device libraries can be used for the identification of devices and their attributes for device research and surveillance within CRNs. The libraries enable focus on an individual device, device categories, or device characteristics. The libraries can also enhance the capacity of the FDA's GUDID for research and surveillance. An example of CRN implementing this tool is the International Consortium of Orthopedic Registries (ICOR) CRN with its device library: The ICOR device library is a global, standardized classification system of hip and knee implantable devices, and includes all their clinical attributes and characteristics to advance the implementation of unique device identifiers and FDA post-market surveillance.[15]

Data Linkage Tools

To advance linkages between registries and routinely available data sources (e.g. claims and administrative data), we developed and refined anonymous linkage algorithms to augment the research capacities of CRNs by bringing together registries, claims data, and electronic health records. Data linkage with indirect identifiers is reliable with high sensitivity and accuracy. It is a cost-effective way to obtain long-term outcomes and has positive implications for long-term device surveillance. The tools have been implemented for Orthopedic CRN[16] and Vascular CRN[17].

[15] International Consortium of Orthopedic Registries (ICOR) Initiative, MDEpiNet. https://www.mdepinet.net/icor. Accessed Dec 2022.

[16] Mao J, Etkin CD, Lewallen DG, Sedrakyan A. Creation and Validation of Linkage Between Orthopedic Registry and Administrative Data Using Indirect Identifiers. *J Arthroplasty.* 2019;34(6):1076-1081.e1070.

[17] Columbo JA, Sedrakyan A, Mao J, et al. Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients. *J Vasc Surg.* 2019;70(3):741-747.

Orthopedic CRN: Creation and Validation of Linkage Between Orthopedic Registry and Administrative Data Using Indirect Identifiers

Vascular CRN: Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients

Return on Investment Tools

The use of CRNs and RWD aid in overcoming many limitations associated with post-market studies and may also reduce the costs and save time for evidence generation. To demonstrate the Return on Investment (ROI) of CRNs, methodologies calculating the ROI and Days Saved among necessary regulatory studies conducted in CRNs compared to those conducted in the absence of CRNs were developed.[18,19] These methodologies aid in the evaluation of CRNs, demonstrate of favorable ROI, and emphasize the value of RWD sources. The effort is being currently implemented in Abdominal Core Health CRN.

Publications:

Determining value of Coordinated Registry Networks (CRNs): a case of transcatheter valve therapies

Use of data from the Vascular Quality Initiative registry to support regulatory decisions yielded a high return on investment

Patient Partnership Development

Patients are an important partner in the MDEpiNet public-private partnership and a critical voice in many of MDEpiNet projects. MDEpiNet patient partners work alongside clinicians, researchers, device manufacturers, FDA, and other federal agency staff to develop and improve real-world data collection and analysis in a variety of clinical areas. Patient partners are identified for CRN or a clinical area through a working group and included in the decision-making process for project-related tasks like 1) roundtable meetings 2) mCDE development 3) stakeholder

[18] Pappas G BJ, Avila-Tang E, et al. Determining Value of Coordinated Registry Networks (CRNs): a case of transcatheter valve therapies. *BMJ Surgery, Interventions, & Health Technologies.* 2019;1:e000003. doi: 10.1136/bmjsit-2019-000003

[19] Cronenwett JL, Avila-Tang E, Beck AW, et al. Use of data from the Vascular Quality Initiative registry to support regulatory decisions yielded a high return on investment. *BMJ Surgery, Interventions; Health Technologies.* 2020;2:e000039.

engagement meetings. Women's health technologies CRN clinical are such as pelvic organ prolapse and uterine fibroids,[20] and Temporomandibular Joint CRN have implemented such partnerships in establishing their core minimum dataset as well as conducting patient-led roundtable meetings to engage key stakeholders.[21]

Delphi Consensus Survey

To facilitate consensus on important aspects of registry advancement, we encouraged the CRNs to follow the Delphi method for structured decision-making by a group of key stakeholders.[22] Undergoing a Delphi process is a preferred method for reaching concordance about a core minimum dataset as traditional consensus panel approaches have challenges such as bias and lack of anonymity. As a result, the Delphi process was conducted to achieve consensus while minimizing the bias inherent in group dynamics and face-to-face responses in the SPARED CRN,[23], WHT[24] and TMJ CRN.[25] Several manuscripts featuring the final core minimum datasets were published in BMJ-SIT.[26,27,28,29,30,31]

[20] MDEpiNet Women's Health Technology CRN. https://www.mdepinet.net/womenshealth. Accessed 22, April 2022.
[21] Kusiak Jea. *The TMJ Patient-Led RoundTable: A History and Summary of Work.* TMJ Association: TMJ Association;2018.
[22] Medical Device Epidemiology Network - Delphi to establish CRN core minimum dataset https://www.mdepinet.net/delphi. Accessed 19 May 2022.
[23] Golan R, Bernstein A, Sedrakyan A, et al. Development of a Nationally Representative Coordinated Registry Network for Prostate Ablation Technologies. *J Urol.* 2018;199(6):1488-1493.
[24] (MDEpiNet), USFDA. The Women's Health Technology Coordinated Registry Network (WHT-CRN). 2019.
[25] MDEpiNet Temporomandibular CRN. https://www.mdepinet.net/tmj. Accessed 15 May22.
[26] LeRoy H, Gressler LE, Liebeskind DS, Brooks CE, Siddiqui A, Ansari S, Sheldon M, Pena C, Sedrakyan A, Marinac-Dabic D. Developing the foundation for assessment of Devices used for Acute Ischemic Stroke Interventions (DAISI) using a Coordinated Registry Network. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000113. doi: 10.1136/bmjsit-2021-000113. PMID: 36393891; PMCID: PMC9660605.
[27] Baird CE, Guiahi M, Chudnoff S, Loyo-Berrios N, Garcia S, Jung M, Gressler LE, Mao J, Hodshon B, Sedrakyan A, Andrews S, Colden K, Roberts J, Anderson A, Sewell C, Marinac-Dabic D. Building Blocks for the Long-acting and Permanent Contraceptives Coordinated Registry Network. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000075. doi: 10.1136/bmjsit-2020-000075. PMID: 36393889; PMCID: PMC9660629.
[28] Baird CE, Myers E, Jacoby V, Gressler LE, Venable S, O'Neill A, Price V, Lee A, Roberts J, Andrews S, Sedrakyan A, Marinac-Dabic D. Development of a core minimum data set to advance real-world evidence generation for uterine fibroids treatment technologies. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000094. doi: 10.1136/bmjsit-2021-000094. PMID: 36393887; PMCID: PMC9660574.
[29] Gressler LE, Devlin V, Jung M, Marinac-Dabic D, Sedrakyan A, Paxton EW, Franklin P, Navarro R, Ibrahim S, Forsberg J, Voorhorst PE, Zusterzeel R, Vitale M, Marks MC, Newton PO, Peat R. Orthopedic Coordinated Registry Network (Ortho-CRN): advanced infrastructure for real-world evidence generation. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000073. doi: 10.1136/bmjsit-2020-000073. PMID: 36393890; PMCID: PMC9660599.
[30] Baird CE, Chughtai B, Bradley CS, *et al*. Development of a coordinated registry network for pelvic organ prolapse technologies. *BMJ Surgery, Interventions, & Health Technologies* 2022;**4:**e000076. doi: 10.1136/bmjsit-2020-000076
[31] Long C, Tcheng JE, Marinac-Dabic D, *et al*. Developing minimum core data structure for the obesity devices Coordinated Registry Network (CRN). *BMJ Surgery, Interventions, & Health Technologies* 2022;**4:**e000118. doi: 10.1136/bmjsit-2021-000118

Data Standardization/ Minimum Core Data Elements/ Harmonization Tools:

The minimum core datasets are drafted by the subject matter experts in each CRN. Once the concepts are drafted, they are modeled in Enterprise Architect (a Unified Modeling Language (UML) tool) as class diagrams. Each data element is assigned to one or more data class(es) within the clinical workflow. If a data element is included in the common clinical data set (i.e., common across CRNs) it will be referenced in the CRN-specific model. All CRN-specific data elements are modeled in the CRN-specific model as a data class, class attributes, or included as a value set. The use of a standardized process to define and map to existing exchange and terminology standards enables the development of clinical domain technical specifications (e.g., FHIR® Implementation Guides). An example is a Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD)[17] intended to improve the quality, utility, and portability of electronic laboratory data (i.e., in vitro diagnostic [IVD] data) through the harmonized implementation of semantic data standards that have been appropriately qualified by a sole authoritative source. In conjunction with SHIELD, the LOINC – IVD Test Code (LIVD) Mapping FHIR® IG was developed to address the needs of the COVID-19 pandemic.

Different CRNs are at the different stages of the development. For example, mCDEs have been developed for SPARED CRN and Women's Health Technologies CRN (see *core minimum dataset section above*). The modeling is being completed for the RAPID PAD project, TMJ CRN and VANGUARD CRN. The RAPID PAD domain instantiated the clinical workflow context needed by all CRNs, TMJ augmented the clinical workflow model with patient-reported information, and VANGUARD developed auxiliary UDI (i.e., clinically relevant) device identification information.

A framework for evidence evaluation and methodological issues in implantable device studies

Active Surveillance Tools:

To support long-term device surveillance we advanced active surveillance methodologies for CRNs. We developed flexible tool to provide users with timely and comprehensive evaluations of medical device safety signals. There are already

various projects underway that use an integrated tool to implement DELTA and other outlier detection in CRNs.[32]

Challenges in outlier surgeon assessment in the era of public reporting

Evidence Review and Synthesis Methodologies:

Systematic literature review is an important tool to identify the gaps and prioritize the research using CRNs. The studies are reviewed by experts using Medline, Embase, Cochrane Controlled Trials Register, reference lists of articles, annual reports of major registries, summaries of safety and effectiveness for pre-market application, and mandated post-market studies at the FDA. This process has shown success when used to complete a literature review on orthopedics devices.[33]

Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies

VALIDATION OF CLAIMS DATA AND LIBRARY OF ICD-9 AND ICD-10 CODES

To facilitate device research in the contemporary era, adapting to the transition from ICD 9 to ICD 10 is critical. Various conditions and events have been defined and translated to ICD 10 algorithms to support research based on CRNs. The clinical accuracy of ICD 9, ICD 10, and CPT codes is at times unknown, although critical to the device and comparative effectiveness research. Validation studies of these coding definitions have been implemented to verify their clinical accuracy. An example of CRN implementing such tool is VISION CRN in the comparison of reintervention rates after endovascular aneurysm repair between the Vascular Quality Initiative registry and data from various sources.[34]

[32] Mao J, Resnic FS, Girardi LN, Gaudino MF, Sedrakyan A. Challenges in outlier surgeon assessment in the era of public reporting. *Heart.* 2019;105(9):721-727.
[33] Nieuwenhuijse MJ, Nelissen RG, Schoones JW, Sedrakyan A. Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies. *Bmj.* 2014;349:g5133.
[34] Columbo JA, Kang R, Hoel AW, et al. A comparison of reintervention rates after endovascular aneurysm repair between the Vascular Quality Initiative registry, Medicare claims, and chart review. *Journal of vascular surgery.* 2019;69:74-79.e76.

A comparison of reintervention rates after endovascular aneurysm repair between the Vascular Quality Initiative registry, Medicare claims, and chart review

DISTRIBUTED ANALYTICAL METHODOLOGIES:

Steps were taken to develop methodologies that enable the distributed analysis of international data. In this approach, standardized data extraction is implemented and distributed to participating registries. Each registry then completes the analyses of its own registry and completely de-identified data summaries are sent back to the coordinating center. Data are then combined using multivariable hierarchical models to evaluate comparative outcomes of devices regarding the main patient-centered outcomes. An example of a CRN that has implemented this effort is the International Consortium of Orthopedic Registries (ICOR) CRN.[6,23]

The International Consortium of Orthopaedic Registries: overview and summary

OBJECTIVE PERFORMANCE CRITERIA (OPC)[35] DEVELOPMENT:

OPC is a numerical target value of safety or effectiveness endpoints derived from historical data from various data sources, such as clinical studies and/or registries. OPCs may be used in single-arm device evaluation that has regulatory implications. In collaboration between the FDA, MDEpiNet and NESTcc[36], advanced methods were developed to construct OPCs, combining estimates obtained from different approaches, ranging from direct analysis of registry or claims data to those reported

REGULATORY HIGHLIGHTS

CRN model was successfully applied to the development of the benchmarks for outcomes of mature orthopedic devices such as those used in hip and knee arthroplasties. Combining data from registries, claims and published literature enabled the construct of Objective Performance Criteria (OPCs) that can be used to reduce the need for concurrent comparison groups in future studies.

[35] Gressler, Laura Elisabeth et al. "Creation of objective performance criteria among medical devices." *BMJ surgery, interventions, & health technologies* vol. 4,1 e000106. 1 Aug. 2022, doi:10.1136/bmjsit-2021-000106

[36] Developing Objective Performance Criteria (OPC) for Outcomes after Hip and Knee Replacements. NESTcc, 16 December 2020 https://nestcc.org/developing-opc-after-knee-hip-replacements/

in the literature. This effort has been implemented in Orthopedic CRN and the manuscript has been accepted in the peer-reviewed journal International Journal of Surgery.[37]

NATURAL LANGUAGE PROCESSING (NLP) APPLICATIONS:

NLP is a valuable method that can be used to parse unstructured text data and extract information from it, including medical notes, radiology reports, and device adverse event reports. For processing a large amount of text data, NLP is efficient and labor-saving. As an example, in the SPARED CRN, we assessed adverse events related to hysteroscopic sterilization device removal using NLP, and extracting information from prostate cancer biopsy reports, magnetic resonance imaging, and partial gland ablation operative reports.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING:

To facilitate the evaluation of patient outcomes and predictors in the context of medical devices, machine learning and other artificial intelligence methods were examined and utilized. Machine learning methods have the advantage of considering complex interactions between predictors to help identify patient populations among whom the treatment works best. This information may aid clinicians in understanding population-specific treatment effects better and assist with clinical decision-making. Examples of CRNs implementing these efforts are women's health, where we examined long-term outcomes after mesh-based sling device use in stress urinary incontinence using a longitudinal discharge database in the New York State,[38] and cardiac, where we examined in-hospital mortality after using Extracorporeal membrane oxygenation (ECMO) using a longitudinal discharge database in the New York State and National Inpatient Sample.

Long-Term Safety with Sling Mesh Implants for Stress Incontinence

[37] Nieuwenhuijse MJ, Randsborg PH, Hyde JH, Xi W, Franklin P, Kazemzadeh-Narbat M, Sun L, Zheng X, Banerjee S, Mao J, Aryal S, Chen A, Liebeskind A, Bonangelino P, Voorhorst P, Devlin V, Peat R, Gressler LE, Marinac-Dabic D, Paxton E, Sedrakyan A. Evidence Based Objective Performance Criteria for Evaluation of Hip and Knee Replacement Devices and Technologies. *International Journal of Surgery ()*: April 10, 2023. https://doi.org/10.1097/JS9.0000000000000169.
[38] Chughtai B, Mao J, Matheny ME, Mauer E, Banerjee S, Sedrakyan A. Long-Term Safety with Sling Mesh Implants for Stress Incontinence. *J Urol*. 2021;205(1):183-190.

MDEPINET HIVE:

MDEpiNet-HIVE is a technology that provides a secure healthcare biomedical data archival ecosystem. MDEpiNet-HIVE maintains a standardization and harmonization framework, high-performance analytics, and an integrator platform.[39] MDEpiNet is leveraging HIVE platform to host registry and claims data and conducting data linkages that are distributed and centralized to support national and international collaborations. HIVE is a distributed storage and computation environment and multi-component cloud infrastructure.

- HIVE provides secure web access for authorized users to deposit, retrieve, annotate, and compute biomedical big data.
- HIVE allows users to analyze the outcomes using web interface visual environments appropriately built-in in collaboration with internal and external end-users.
- HIVE integrates patient-facing mobile apps to collect patient-reported outcomes.
- HIVE supports registry development as a centralized platform.

There are various featured projects utilizing HIVE infrastructure and technology. A customized FHIR app for projects such as stress urinary incontinence and pelvic organ prolapse repair was established in the WHT CRN. These are being tested on mobile and connected devices through work with clinical teams to finalize the data elements for terminology and to refine the app with feedback on usability, including 1) Case report forms to collect data from registry partners for prospective ICVR projects of ruptured abdominal aortic aneurism (AAA). SPARED CRN registry development; 2) TMJ CRN registry development and pilot study; and 3) Pediatric scoliosis PRO study in Orthopedic CRN.

Mobile Apps:

The Mobile Apps engine integrated with HIVE technology provides novel and robust means of capturing data through patient-facing and physician-facing portals. Various HIVE projects in women's health technologies[40] and cancer settings, peripheral disease were conducted. Patient and physician registry platforms were developed to

support national and international collaborations. HIVE implantation is ongoing for Pediatric Scoliosis patient facing portal.

Development and Usability Testing of a Mobile Application to Monitor Patient-Reported Outcomes after Stress Urinary Incontinence Surgery

Blockchain is a novel technology that advances data safety, security, and reliability through the (1) assurance of immutable data provenance, (2) implementation of smart contracting, and (3) implementation of the electronic consent form and helps build trust with a diverse group of stakeholders. These aspects of blockchain enable various stakeholders to share their data within an ecosystem, which in turn can increase the velocity of research. A pilot for utilizing blockchain to store data in HIVE for MDEpiNet was completed that could be utilized by various CRNs in their infrastructure.[41] In TMJ CRN, a pilot study is focused on securing and deidentifying patient information using blockchain technology.

OBJECTIVE 2

Pilot test and refine the existing device- specific Fast Healthcare Interoperability Resources (FHIR) profiles (produced as part of a FY17 OS-PCORTF project) in an expanded set of three to five CRNs to demonstrate the capture and exchange of CRN data using FHIR.

2A – CRN DATA EXCHANGE

Report submitted for publication on the FDA website, MDEpiNet website and/or as a journal manuscript. The report will include the goals, methods, deliverables, lessons learned from pilots and potential future opportunities regarding the capability of CRNs to exchange data using FHIR

The goal of the CRN data exchange is to continue building on the previous Women's Health Technologies Coordinated Registry's (WHT-CRN) Pelvic Organ Prolapse (POP) pilot, which implemented based on specifications in the WHT-CRN Implementation Guide (IG). The lessons learned from this pilot included: the need to: 1) leverage existing FHIR® Implementation guides,

[39] MDEpiNet HIVE. https://www.mdepinet.net/hive. Accessed 28 April 2022.
[40] Chughtai B, Cho A, Simonyan V, et al. Development and Usability Testing of a Mobile Application to Monitor Patient-Reported Outcomes after Stress Urinary Incontinence Surgery. *Urology*. 2022;159:66-71.
[41] MDEpiNet Blockchain and Artificial Intelligence Task Force (BAIT). https://www.mdepinet.net/bait. Accessed 22 April 2022.

profiles and implementation patterns, 2) enhance FHIR® resources, value sets and extensions available, especially for device-related use cases, and 3) build new FHIR® Core and CRN-specific FHIR® Profiles that will expand the portfolio of standards.

Leverage existing FHIR® Implementation Guides, their profiles and specific implementation patterns.

The WHT-CRN IG demonstrated that the US-Core FHIR® IG (based on the US Core Dataset of Interoperability (USCDI) and the ONC 2015 Edition EHR Certification Criteria (2015 Edition)) could be leveraged across multiple use cases. In addition, the Structured Data Capture IG (i.e., Questionnaire and Questionnaire Response resources) as well as the Patient Reported Outcomes (PRO) FHIR® IG was used to collect additional data during the pilot. These underlying standards and the common clinical data sets are being leveraged and set the foundation for the other CRNs' clinical concepts that need to be covered for device-related procedures. Each CRN needs to work with clinical team to determine/refine/finalize the data elements and terminology in order to map them into the standards mentioned above.

In addition, it was identified that the Unique Device Identification (UDI) minimum core data elements was not consistently represented across the healthcare exchanges (i.e., other FHIR® IGs). These inconsistencies have since been addressed in the core resources and development of a FHIR® Implementation Guide for UDI Exchange has begun.

Based on these lessons learned, the project team identified additional exchange requirements – including: the need to include additional device characteristics that are clinically relevant, and the need to expand beyond the US Core IG that applies too many constraints.

Enhance FHIR® Resources, value sets and extensions to enable additional use cases

With each new clinical specialty, there is a need to identify and align the minimum core data elements to the FHIR® Resources available. Given that the US Core is based on FHIR® R4, the unique device identification profile is

specific to implantable medical devices. The FHIR® R4 Device resource required enhancements to capture additional device characteristics – i.e., clinically-relevant properties and/or settings. In addition, the FHIR® Device Usage resource was not available to describe some of the specific data elements for device usage in the WHT clinical domain. During the course of this project, the FHIR® Device and Device Usage resources were enhanced to include additional physical device characteristics, properties and classifications based on the requirements from several CRN minimum core data elements defined by VANGUARD CRN, TMJ-CRN, Robotics CRN, ESKD CRN, as well as some of the more mature CRNs – e.g., VISION. These enhancements will be included in FHIR® R5 and available for use and development of FHIR® Profiles and/or included in FHIR® Implementation Guides based on that version of the standard.

Build new FHIR® Core and CRN-specific FHIR® *Profiles*

Specifically, this area of improvement addresses the requirement to continue refining and expanding on the FHIR® Profiles that were previously defined in FY17 OS-PCORTF project. In order to enable the progression of maturity of CRNs in several domains of the CRN Maturity Framework (outlined in Objective 1), a common representation of data elements (specifically device identification data) across CRNs is needed. The key development of FHIR® Profiles for use by CRNs include identification of devices implanted in a patient during a procedure, insertion of a medical device in a patient for venous access, use of a reusable, reprocessed or multi-use device during a procedure, patient and provider exposure to a device that may emit harmful gases or radiation, and use of a device that is measuring key clinical data during a procedure.

These FHIR® Profiles will enable interoperability within and across the healthcare ecosystem by converging on a standardized exchange mechanism.

Refer to Objective 2B below for the use of FHIR® Profiles in FHIR® Implementation guides and Objective 1C above for work related to

identifying the minimum core data elements that need to be supported by these exchange standards.

2B – IMPLEMENTATION GUIDES

Refined FHIR implementation guide (for a wider set of CRNs) for exchange of clinical data (including UDI and clinically meaningful device attributes) and administrative data to support device evaluation

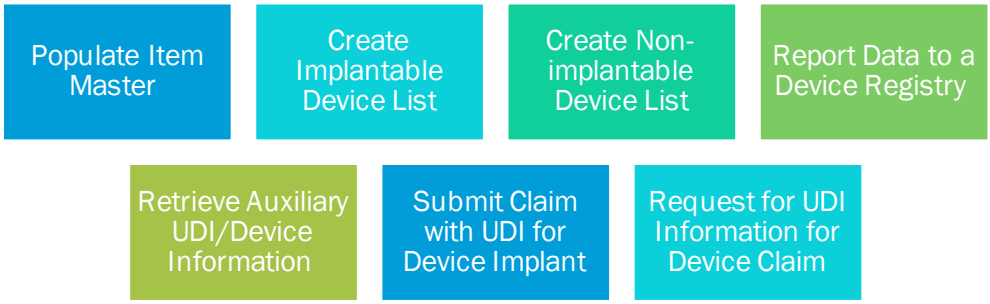
The FHIR® Unique Device Identification (UDI) Exchange Implementation Guide

The scope of the FHIR® Unique Device Identification (UDI) Exchange Implementation Guide (IG) is to enable consistent device identification and device usage across the healthcare ecosystem. In addition, the IG enables domain-specific implementation guides to follow documented guidelines for UDI Exchange and support interoperability across various domains. This includes continuing care across device, disease, and patient life cycles; device safety and effectiveness evaluation; cost and claims information; and quality analysis.

The FHIR® Unique Device Identification (UDI) Exchange IG is a cross-paradigm IG mainly focusing on the FHIR® standard but also includes representation of UDI in the other HL7 base standards (v2 and C-CDA) in order to provide consistent implementations across the HL7 product lines.

Given that the promotion of unique device identification (UDI is the first domain within the CRN Maturity Framework and is a key to enable health IT to exchange of the UDI.

The FHIR® UDI Exchange IG is based on a UDI Logical data model that includes the device identification profiles and/or extensions to support the scenarios targeted by this implementation guide. The Initial focus is to provide specific guidance for the following scenarios:



Additional guidance is envisioned to address high-level scenarios for the following:

- Enable Interoperability exchanges
- Report UDI Regulatory Information
- Additional supply chain exchanges

The FHIR® Profiles outlined in Objective 2A, serve as the core artifacts in the FHIR® UDI Exchange IG, which address the scenarios above. In addition, further adoption of this IG for device identification and usage will enable: 1) access to structured device information in clinical documents, 2) support for enhanced post market surveillance, 3) ability to perform targeted recalls, 4) clinical decision support, and 5) use of real-world device identification data for analysis/research.

The VANGUARD CRN FHIR® Implementation Guide

The VANGUARD CRN FHIR® Implementation Guide is intended to leverage the standards work completed by the WHT CRN and expand to the clinical concepts for venous access catheter related infections. Specifically, this FHIR® IG will leverage the device identification and characteristics outlined in the FHIR® UDI Exchange IG; and add the additional data elements necessary to capture venous access catheter related infections during procedures in an inpatient setting. The draft data elements are included in

Appendix 3: Minimum Core Data Sets, and will be expanded for other healthcare settings and/or venous access devices.

Summary

The FHIR® WHT-CRN IG, UDI Exchange IG and VANGUARD IG will all serve different aspects of the CRN exchanges ranging from structured data capture, device-specific data exchanges, procedure and event related data and finally query mechanisms to create infrastructural components for other CRNs to use as they mature into their own implementations and specialty-specific requirements.

OBJECTIVE 3

Pilot test and refine the instrument for capturing patient preferences from in at least one clinical area (e. g. End Stage Kidney Disease – ESKD) to evaluate scientifically valid data regarding patient uncertainty in accepting a variety of benefit/risk tradeoffs within a CRN.

3A – PATIENT PREFERENCE INSTURMENT

Instrument for capturing patient preferences in one clinical area (e.g. ESKD). Report submitted for publication on the FDA website, MDEpiNet website and/or a journal publication detailing how patient preference data can be collected and incorporated into CRNs

The aim of this project was to examine how patients trade potential benefits and risks of future wearable dialysis devices, and how patient preferences differ based on the patient's circumstances, unique characteristics, and treatment modalities. The second objective of this project was to evaluate the ability of the ESKD CRN infrastructure to collect PPI regarding RRT using an existent survey instrument and to map the survey fields to clinical data elements in HIVE. These accomplishments will benefit future kidney replacement therapeutics (KRT), including the creation of innovative therapeutics or alternatives to current dialysis methods.

Demographic information: Age, Country, State of Residence, Birth Sex or Administrative Gender, Gender Identity, Ethnicity, Race, Education Level, Employment status

Past Medical History: Duration of Dialysis Treatment, In-center hemodialysis treatment History, Home hemodialysis History, Peritoneal Dialysis History, Kidney Transplant History, Dialysis Treatment, Dialysis Treatment Start Date

Condition-specific awareness and preference: Wearable Device Awareness, Source of Wearable Device Awareness, Treatment Option Ratings, Disconnected catheter, fistula or graft accidentally, Risk of Serious Bleeding, Risk of Serious Bleeding compared to other people receiving dialysis, Serious Infection, Risk of Serious Infection, Risk of Serious Infection compared to other people receiving dialysis; Treatment (In-center versus wearables) Preference based on variable levels of risk.

The survey instrument was developed in collaboration with Kidney Health Initiative (KHI) and RTI. The online survey was administered to approximately 600 patients over a period of four months and included various recruitment methods (e.g., social media, direct outreach, outreach at the point of care, and through patient advocacy

organizations). The respondents only included patients receiving in-center hemodialysis, home hemodialysis or peritoneal dialysis. The survey included specific instructions and education to ensure the respondents were provided information about the treatment options and differences in devices and/or risks associated with them. The results the final survey results from the 54-item web-based instrument yield estimates of the maximal acceptable risk for the described wearable device and willingness to wait for wearable devices with lower risk. In addition, it may inform considerations for future technology advancements in devices and the patient preferences for them.

The focus of this patient preference-driven manuscript[42] was to determine the patient's perceived risk of blood loss or infection based on the type of treatment and/or device options. The goal was to understand what level of risk patients are willing to take based on the options of In-Center treatment versus wearable devices (and minimal visits to the treatment center).

The survey instrument used during the initial study (as reported above) that was implemented as a prototype has been transferred to the HIVE environment to enable its broader use. The additional question types for preference thresholds were developed and will be available for other CRNs to use with other devices and/or treatment options. HIVE includes data entry capabilities that help reduce the amount of missing data, promotes the entry of valid high-quality data while reducing the burden and time associated with data entry. This RRT PPI survey also

The HIVE infrastructure enables the secure collection and storage of data via a flat "honeycomb model" where data is persisted in multiple table columns and mapped into a flat, but structured table. In addition the data entry features reduce the amount of missing data, promotes the entry of valid high quality data while reducing the burden and time associated with data entry.

[42] Flythe JE, Forfang D, Gedney N, White DM, Wilkie C, Cavanaugh KL, Harris RC, Unruh M, Squillaci G, West M, Mansfield C, Soloe CS, Treiman K, Wood D, Hurst FP, Neuland CY, Saha A, Sheldon M, Tarver ME. Development of a Patient Preference Survey for Wearable Kidney Replacement Therapy Devices. Kidney360. 2022 May 5;3(7):1197-1209. doi: 10.34067/KID.0001862022. PMID: 35919522; PMCID: PMC9337889.

included various educational and instructive question types that leverage additional technical capabilities for data validation and confidence levels on the user's ability to respond to the new question types. In addition, the HIVE implementation leverages existing visual and auditory tools to provide the instructive information as pre-survey tutorials instead of embedding them into the survey instrument in plain text. These new features are being developed in the HIVE infrastructure and will be tested with the ESKD population during the pilot phase (outside of this duration of this grant).

After completion of the HIVE ESKD PPI study, the report of the results and findings will be posted. In addition, the infrastructure components will be available to fit any future data collection needs and have a wider applicability for the inclusion of PPI statements in patient and physician-facing mobile applications.

Risk tolerance in the setting of wearable dialysis devices: a patient preference study using the threshold technique

Development of a Patient Preference Survey for Wearable Kidney Replacement Therapy Devices

3B – PATIENT-GENERATED MINIMUM CORE DATA

Minimum Core Data elements derived from pilot implementation of patient-generated information module.

The initial collection of data elements for end-stage kidney disease sets the foundation of existing common elements from USRDS for the current patient population of ESKD CRN and is aligned to the clinical workflow. These elements establish the infrastructure from multiple data sources for high-quality, relevant, and actionable evidence to improve patient outcomes from ESKD-related therapies, including innovative therapeutics and alternatives to dialysis as currently administered, as well as to promote data collection to support exchange of data across therapies, patient populations, locations, and episodes of care.

One of the main data sources for ESKD is the United States Renal Data System (USRDS),[43] which is a national data system which collects, analyzes, and disseminates information on chronic kidney disease (CKD) and end-stage kidney disease. Existing core data sets for CKD include the following: 1) Standardized Outcomes in Nephrology (SONG), which is an international initiative that aims to establish core outcomes in CKD 2) the International Consortium for Health Outcomes Measurement (ICHOM) Standard Set for CKD, which are recommendations established by a group of physicians, measurement experts, and patients, and 3) the European Association of Rehabilitation in CKD recommendations on measurement and interpretation of physical function.[44, 45, 46]

The additional ongoing work takes into consideration emergent data for novel and innovative medical devices for patients with kidney failure. The work includes other treatments to prevent disease progression, including biologics and pharmaceutical therapies.

These patients will generate data for each dialysis treatment encounter, and this may be multiple times a week. The data collected for this population needs to identify key milestone events that will need to be captured. In addition, as new innovative products are developed, some may include automated data collection from the communicating devices.

Note: The initial work on the minimum core data is ongoing and can be used to expand in future work.

[43] CMS. CROWNWeb Data Management Guidelines [Internet]. Available from: https://mycrownweb.org/assets/crownweb-dm/CROWNWeb_Data_Management_Guidelines_FINAL.pdf. Accessed 2022

[44] Kidney Health Initiative. Technology roadmap for innovative approaches to renal replacement therapy [Internet]. 2018; Available from: https://www.asn-online.org/g/blast/files/KHI_RRT_Roadmap1.0_FINAL_102318_web.pdf

[45] Bonventre JV, Hurst FP, West M, Wu I, Roy-Chaudhury P, Sheldon M. A Technology Roadmap for Innovative Approaches to Kidney Replacement Therapies. *Clin J Am Soc Nephrol*. 2019; 14:1539–1547.

[46] Liu FX, Rutherford P, Smoyer-Tomic K, Prichard S, Laplante S. A global overview of renal registries: a systematic review. *BMC nephrology*. 2015; 16:31.

OBJECTIVE 4

Advance CRN capacity to produce linked data sets and to combine heterogeneous data developing machine learning techniques to validate the linked data sets.

The CRN capacity to create the linked data sets depend on many factors including, but not limited to (A) data sources (including registry's maturity in terms of the data capture and complementary data sources available for linkage), (B) data linkages (including validation techniques and methodologies) and (3) analytical tools. The three sections below illustrate the progress made in these building blocks across the CRNs.

4A – DATA SOURCES

Paper published on the MDEpiNet website that includes a catalogue of available data sources/per clinical area that will be available for scientists conducting the PCOR research

The table below summarizes the data sources used across the CRNs and details follow on the resulting research.

Table 4: Summary of Data Sources Used by CRNs

Data Source	CRN	Clinical Category
NIS	Cardiac	
	SPARED	Urology, Prostate cancer
SPARCS	WHT/UG	SUI, UF, POP, LARC
	SPARED	Urology, Prostate cancer
HCAI	SPARED	Prostate cancer, HIFU device outcomes
	Ortho	Total hip/knee arthroplasty gender differences
		OPC development in hip and knee, Total ankle replacement outcomes
MEDPAR	DAISI	Acute Ischemic Stroke
	VISION	SAVR
		TAVR
SEER-Medicare	SPARED	Urology (Prostate cancer, HIFU devices)

	Robotic	Robotic assisted technology in urology, colorectal and thoracic areas

Data sources that are not CRN-specific

NATIONWIDE INPATIENT SAMPLE (NIS)

The National (Nationwide) Inpatient Sample (NIS), developed by the Healthcare Cost and Utilization Project (HCUP), is the largest all-payer inpatient healthcare database in the US.[47] The NIS contains information on all hospital stays, regardless of expected payer, for the hospitalization. The NIS is a 20% sampled discharge record, currently containing sampled data from 48 participating states and the District of Columbia and covering more than 97 percent of the US population. The database contains patient sociodemographic characteristics (e.g., sex, age, race, median household income for ZIP Code), diagnoses, procedures, hospital characteristics (e.g., ownership, teaching status), expected payment source, length of stay, discharge status, and total charges for each hospital stay. The NIS can be used to estimate the utilization of medical devices or device-related procedures in the US, examine safety and other outcomes following device use, and assess trends in the utilization and outcomes of medical devices (see our published studies below).

Topic: Utilization and safety of novel cardiac surgical procedures and devices:

Within the cardiology clinical specialty, the NIS database was queried to investigate national trends and in-hospital outcomes of mechanical versus bioprosthetic prosthesis aortic valve replacement in one publication,[48] while for a second publication, the utilization and safety of robotic-assisted mitral valve repair was assessed by comparing in hospital mortality, complications, length of stay, and cost for patients undergoing robotic-assisted mitral valve repair with patients undergoing nonrobotic procedures.[49] The studies found that the usage of bioprosthetics increased dramatically over time, was safe, and was associated with lower in-hospital mortality.

[47] Overview of the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research Quality (AHRQ). https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed April 22, 2022.
[48] Isaacs AJ, Shuhaiber J, Salemi A, Isom OW, Sedrakyan A. National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements. *J Thorac Cardiovasc Surg*. 2015;149(5):1262-1269.e1263.
[49] Paul S, Isaacs AJ, Jalbert J, et al. A population-based analysis of robotic-assisted mitral valve repair. *Ann Thorac Surg*. 2015;99(5):1546-1553.

"National trends in utilization and in-hospital outcomes of mechanical versus bioprosthetic aortic valve replacements"

"In-hospital outcomes of robotic-assisted mitral valve repair vs. non-robot repair"

Topic: Prostatectomy outcomes:

In the prostate ablation space, NIS was used to evaluate national trends in iatrogenic complications and associated burden of care in patients undergoing robotic prostatectomy versus the traditional open surgery. The findings included an associated lower risk of iatrogenesis and increased safety with the minimally invasive prostatectomy as compared to open surgery.[50]

"In-hospital injury of robotic prostatectomy over time"

NEW YORK STATE STATEWIDE PLANNING AND RESEARCH COOPERATIVE SYSTEM (SPARCS)

Established in 1979, SPARCS is an all-age-group, all-payer data that collects information for every hospital discharge, ambulatory and outpatient surgery, and emergency department admission in New York State.[51] The data contain patient demographics (e.g., age, sex, race, and ethnicity), expected payment source, primary and secondary diagnoses and procedures, and length of stay and charges. A unique personal identifier is assigned to every patient and encrypted to allow longitudinal analyses without compromising the confidentiality of the records. Each hospital and surgeon also have a unique identifier, which allows for the collection of hospital and surgeon-specific data over time in the database, irrespective of the hospital where the surgeon practiced. SPARCS can be used to estimate statewide use and outcomes of medical devices and device-related procedures. As patients' records are longitudinally linkable within the SPARCS data, investigators can examine short

[50] Chughtai B, Isaacs AJ, Mao J, et al. Safety of robotic prostatectomy over time: a national study of in-hospital injury. *J Endourol*. 2015;29(2):181-185.
[51] Statewide Planning and Research Cooperative System (SPARCS). New York State Department of Health. https://www.health.ny.gov/statistics/sparcs/. Accessed 2022.

and long-term cross-institution outcomes of patients, such as readmissions and reinterventions. The SPARCS can also be used to study the impact of facility and physician volumes on device outcomes (see our published studies below).

Topic: Urogynecology mesh use and safety in pelvic organ prolapse and stress urinary incontinence treatment:

SPARCS has largely been utilized for studies in the context of women's health technologies, with the majority of the publications focusing on the safety of urogynecologic mesh implantation for the treatment of several pelvic floor disorders. Short and long-term outcomes, safety and reintervention rates have been assessed for mesh usage versus non-mesh repair for pelvic organ prolapse in women in New York state.[52][53] Additionally, evidence supporting a dose-response relationship between the amount of mesh used and subsequent mesh erosions, complications, and invasive repeated intervention has also been found.[54] Long-term risks, predictors of mesh erosion, and factors indicative of reoperation were also evaluated following urethral sling procedure for urinary incontinence using SPARCS.[55] The results suggested that the highest erosion cases of the urethral sling alone were observed among younger Caucasian women treated at low volume facilities. However, the highest overall erosion was observed when a urethral sling was implanted concomitantly with mesh for the treatment of pelvic organ prolapse.

- *"Use and risks of surgical mesh for pelvic organ prolapse surgery in women in New York state: population-based cohort study"*
- *"Association Between the Amount of Vaginal Mesh Used With Mesh Erosions and Repeated Surgery After Repairing Pelvic Organ Prolapse and Stress Urinary Incontinence"*
- *"Long-term Device Outcomes of Mesh Implants in Pelvic Organ Prolapse Repairs"*
- *"Long-Term Safety with Sling Mesh Implants for Stress Incontinence"*

[52] Chughtai B, Mao J, Asfaw TS, Heneghan C, Rardin CR, Sedrakyan A. Long-term Device Outcomes of Mesh Implants in Pelvic Organ Prolapse Repairs. *Obstet Gynecol*. 2020;135(3):591-598.
[53] Chughtai B, Mao J, Buck J, Kaplan S, Sedrakyan A. Use and risks of surgical mesh for pelvic organ prolapse surgery in women in New York state: population based cohort study. *Bmj*. 2015;350:h2685.
[54] 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.
[55] Chughtai B, Mao J, Matheny ME, Mauer E, Banerjee S, Sedrakyan A. Long-Term Safety with Sling Mesh Implants for Stress Incontinence. *J Urol*. 2021;205(1):183-190.

"Food and Drug Administration Safety Communication on the Use of Transvaginal Mesh in Pelvic Organ Prolapse Repair Surgery: The Impact of Social Determinants of Health"

Topic: Use and outcomes of device-based treatment in benign prostate hyperplasia:

SPARCS, together with California Health Care Access and Information (HCAI) data (described below), was also used in the context of prostate ablation to compare outcomes of the traditional transurethral prostatectomy surgery versus more novel laser options for the treatment of benign prostatic hypertrophy.[56,57,58,59] The studies suggested that although associated with higher risk of short and long-term complications, transurethral prostatectomy remained the most common procedure performed. The higher complication rates of transurethral prostatectomy also extended to multi-morbid (Charlson comorbidity index ≥ 3), as well as elderly (aged ≥ 75) patients with benign prostatic hyperplasia. However, when compared to all three types of laser prostatectomy procedures (coagulation, vaporization, or enucleation), transurethral prostatectomy had a lower rate of long-term reoperation.

"Trends and Utilization of Laser Prostatectomy in Ambulatory Surgical Procedures for the Treatment of Benign Prostatic Hyperplasia in New York State (2000-2011)"

"Safety and Efficacy of Outpatient Surgical Procedures for the Treatment of Benign Prostatic Enlargement in New York State and California (2005-2016)"

[56] Chughtai BI, Simma-Chiang V, Lee R, et al. Trends and Utilization of Laser Prostatectomy in Ambulatory Surgical Procedures for the Treatment of Benign Prostatic Hyperplasia in New York State (2000-2011). *J Endourol*. 2015;29(6):700-706.
[57] Bouhadana D, Nguyen DD, Zhang X, et al. Safety and efficacy of TURP vs. laser prostatectomy for the treatment of benign prostatic hyperplasia in multi-morbid and elderly individuals aged ≥ 75. *World J Urol*. 2021;39(12):4405-4412.
[58] Stoddard MD, Zheng X, Mao J, Te A, Sedrakyan A, Chughtai B. Safety and Efficacy of Outpatient Surgical Procedures for the Treatment of Benign Prostatic Enlargement in New York State and California (2005-2016). *J Urol*. 2021;205(3):848-854.
[59] Raizenne BL, Zheng X, Mao J, et al. Real-world data comparing minimally invasive surgeries for benign prostatic hyperplasia. *World J Urol*. 2022;40(5):1185-1193.

Safety and efficacy of TURP vs. laser prostatectomy for the treatment of benign prostatic hyperplasia in multi-morbid and elderly individuals aged ≥ 75"

"Real-world data comparing minimally invasive surgeries for benign prostatic hyperplasia"

CALIFORNIA HEALTH CARE ACCESS AND INFORMATION (HCAI, FORMERLY OFFICE OF STATEWIDE HEALTH PLANNING AND DEVELOPMENT)

The Department of HCAI collects data from over 7000 licensed healthcare facilities in California.[60] The HCAI patient discharge data (PDD), emergency department data (EDD), and ambulatory surgery data (ASD) contain all-age-group, all-payer data from every hospital discharge, ambulatory and outpatient surgery, and emergency department admission in California. The data contain patient demographics (e.g., age, sex, race, and ethnicity), expected payment source, primary and secondary diagnoses and procedures, and length of stay. Similar to SPARCS, HCAI-PDD, -EDD, and -ASD contain unique identifiers for each patient that enable the assessment of longitudinal patient and device outcomes. These data also contain unique identifiers for facilities. The HCAI data can be used to examine statewide use and short and long-term outcomes of medical devices and device-related procedures; and to study the impact of facility volume on device outcomes (see our published studies below).

Topic: Use and outcomes of device-based treatment in benign prostate hyperplasia (these publications have been discussed under the description of the SPARCS data source):

"Safety and Efficacy of Outpatient Surgical Procedures for the Treatment of Benign Prostatic Enlargement in New York State and California (2005-2016)":

"Safety and efficacy of TURP vs. laser prostatectomy for the treatment of benign prostatic hyperplasia in multi-morbid and elderly individuals aged ≥ 75":

"Real-world data comparing minimally invasive surgeries for benign prostatic hyperplasia":

[60] The Department of Health Care Access and Information (HCAI) California State Department of Health. https://hcai.ca.gov/data-and-reports/. Accessed 2022.

Topic: Sex difference in hip replacement outcomes:

HCAI, together with SPARCS, were utilized to elucidate whether there is an association between sex and early (2-year) revision rates post primary total hip arthroplasty, since there are higher rates of women undergoing this surgery than men.[61] The patient cohort data from the two statewide databases (New York State and California) included patients 18 years or older with osteoarthritis who underwent total hip arthroplasty. The study found no clinically meaningful difference between men and women in all-cause revision rates between men and women two years after primary total hip arthroplasty. Interestingly, the risk of revision in women was moderately higher than in men in a subgroup of patients who were younger than 55 years, were Caucasian, had either Medicare or commercial insurance, or had the index procedure performed at high-volume facilities, suggesting that risk factors should be more closely investigated in younger patients undergoing total hip arthroplasty.

"Association of Sex with Risk of 2-Year Revision Among Patients Undergoing Total Hip Arthroplasty"

100% MEDICARE PROVIDER ANALYSIS AND REVIEW (MEDPAR) FILE AND MASTER BENEFICIARY SUMMARY FILE (MBSF)

The MedPAR database contains information of 100% fee-for-service Medicare beneficiaries using hospital inpatient services. Medicare is the federal health insurance program for US citizens aged 65 or older, and younger patients with disabilities or with end-stage renal diseases. In recent years, about 60% Medicare beneficiaries are enrolled in fee-for-service Medicare. All Medicare FFS beneficiaries received Part A benefits which cover inpatient stays. MedPAR consolidates Inpatient Hospital and Skilled Nursing Facility (SNF) claims data. MedPAR data contain patient demographics (e.g., age, sex, race, and ethnicity), expected payment source, primary and secondary diagnoses and procedures, and length of stay. MedPAR data also include extensive claims data, such as charges and costs incurred during the hospitalization and payments made by Medicare. Each hospital has a Medicare

[61] Chen A, Paxton L, Zheng X, et al. Association of Sex With Risk of 2-Year Revision Among Patients Undergoing Total Hip Arthroplasty. *JAMA network open.* 2021;4:e2110687.

facility identifier. MBSF contains Medicare beneficiaries' demographics, residence (mailing zip code and residential county and state), enrollment in Medicare, and death information. Death date is validated for 99% of Medicare beneficiaries. Across all Medicare files, each beneficiary has a unique encrypted Bene ID that allows longitudinal tracking of patients' records, enrollment, and death. MedPAR and MBSF are valuable in the assessment of national utilization and outcomes of medical devices among Medicare beneficiaries. Short and long-term outcomes can be examined with MedPAR and MBSF data, such as readmissions, reinterventions, and all-cause mortality. MedPAR and MBSF can also be used to study the impact of facility volume on device outcomes (see our published studies below).

Topic: Use of clipping and coiling for unruptured intracranial aneurysms:

Endovascular coiling is an increasingly popular treatment for the obliteration of unruptured intracranial aneurysms. Risks exist for all age groups (stroke, transient ischemic attack, hemiparalysis, hematoma, etc.), but older patients face particularly higher procedural risks and higher chances that an untreated aneurysm may rupture and cause subarachnoid hemorrhage. In this context, MEDPAR data from 2000-2010 was used to assess trends and outcomes in clipping and coiling of unruptured intracranial aneurysms and in subarachnoid hemorrhage among Medicare patients. It was found that although outcomes tended to improve over time (30-day mortality, in-hospital complications, and 30-day readmissions decreased over the 10-year span, generally reaching their lowest levels in 2008 to 2010), increased preventative treatment of unruptured intracranial aneurysms did not result in a population-level decrease in subarachnoid hemorrhage rates.[62]

"Clipping and Coiling of Unruptured Intracranial Aneurysms Among Medicare Beneficiaries, 2000 to 2010"

Topic: Hospital aortic valve replacement volume and TAVR outcomes:

Although Medicare and Medicaid national coverage determination for a transcatheter aortic valve replacement (TAVR) includes volume requirements for surgical aortic valve replacement (SAVR) for hospitals seeking to initiate or continue TAVR programs. However, very little is known regarding the association between the

[62] Jalbert JJ, Isaacs AJ, Kamel H, Sedrakyan A. Clipping and Coiling of Unruptured Intracranial Aneurysms Among Medicare Beneficiaries, 2000 to 2010. *Stroke.* 2015;46(9):2452-2457.

SAVR volume and the TAVR outcomes in medical institutions. The study found that hospitals with a high SAVR volume are most likely to be fast adopters of TAVR, but hospital SAVR volume alone is not associated with better TAVR outcomes. Interestingly, high volume TAVR hospitals are associated with lower mortality rates, especially when these hospitals also have high SAVR volumes.[63]

"Association Between Hospital Surgical Aortic Valve Replacement Volume and Transcatheter Aortic Valve Replacement Outcomes"

SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS PROGRAM (SEER)-MEDICARE

SEER-Medicare is a linked database of the SEER registry and Medicare claims data.[64] Funded by National Cancer Institute (NCI) since 1973, SEER is an authoritative cancer surveillance program in the US. Medicare is the federal health insurance program for US citizens aged 65 or older, and younger patients with disabilities or with end-stage renal diseases. The SEER-Medicare linkage augmented SEER registry data with long-term follow-up from Medicare claims, first completed in 1991. It was based on individual identifiers and was updated every two years recently.

As of 2021, SEER collects cancer incidence and survival through 28 population-based registries in 22 US geographic areas, covering approximately 48% of the US population. The 28 registries routinely collect basic demographics of patients, including age, sex, race and ethnicity, residential location (metropolitan/urban/rural), and the reporting SEER registry. SEER records up to 10 primary cancers for each patient. For each cancer, the data contain granular details about patients' cancer characteristics at baseline, including diagnosis year and month, tumor stage, grade, histology, behavior, size, lymph node involvement, distant metastasis. SEER also contains patients' survival and causes of death.

Medicare files included in SEER-Medicare are Medicare Provider Analysis and Review (MEDPAR), master beneficiary summary file (MBSF), outpatient and physician claims, part D prescription claims, home health agency claims, and durable medical equipment claims. All Medicare FFS beneficiaries received Part A

[63] Mao J, Redberg RF, Carroll JD, et al. Association Between Hospital Surgical Aortic Valve Replacement Volume and Transcatheter Aortic Valve Replacement Outcomes. *JAMA Cardiol*. 2018;3(11):1070-1078.
[64] SEER-Medicare Linked Datasets. NCI, Division of Cancer Control and Prevention. Healthcare Delivery Resarch Program Web site. http://healthcaredelivery.cancer.gov/seermedicare/. Accessed 2022.

benefits which cover inpatient stays. 96% of the beneficiaries also enroll in Medicare part B for benefits covering outpatient care and doctors' services. Medicare implemented part D benefit in 2006 to help beneficiaries pay for outpatient prescription drugs purchased at retail. Approximately 70% of fee-for-service beneficiaries enrolled in Part D. Medicare files contain diagnoses and procedures that patients received in inpatient, outpatient, ambulatory, and office settings. MBSF contains Medicare beneficiaries' demographics, residence (residential county and state), enrollment in Medicare, and death information. Death date is validated for 99% of Medicare beneficiaries. For beneficiaries enrolled in Part D, oral medication prescriptions can be identified from Part D claims. Auxiliary files include census data, hospital characteristics file, and physician characteristics file. Census data contain socio-economic information on zip code and tract levels, such as median household income, education attainment, and proportion of residents in poverty. The hospital characteristics file contains information about hospitals that are part of the SEER-Medicare data, such as type of ownership, bed size, teaching status, and NCI designation. The physician characteristics file contains measures concerning providers such as sex, specialty, place of service, and geography.

Each patient in SEER-Medicare has a unique identifier that allows longitudinal analysis. Hospital and physician identifiers are also included but encrypted. These identifiers can be linked to the hospital and physician characteristics file to obtain hospital and physician characteristics. Using combined data from SEER and Medicare, investigators can examine short-term and long-term outcomes, such as readmission, reintervention or retreatment, and all-cause and cancer-specific mortality, after device-based cancer treatment. Investigators can also assess costs and healthcare resource use associated with device-based cancer treatment. In addition, the association between hospital and physician characteristics and patient and device outcomes can be examined using SEER-Medicare data.

We currently obtained the most recent data linkage for this analysis (2020 version). In this linkage, three new SEER registries were added: Idaho, Massachusetts, and New York, bringing the SEER coverage to approximately 37% of the US population compared to the 28% in the previous linkage. Data we obtained included cancer

incidence from 1975 to 2017 and Medicare claims from 2006 to 2019 and contained gastrointestinal, lung, and renal cancers.

Topic: Comparative studies of lung-cancer treatments (e.g., thoracoscopic surgery, SABR):

In the lung cancer clinical space, SEER-Medicare was probed to draw comparisons in survival rates (as well as cancer-specific survival) of Medicare patients undergoing thoracoscopic lung resection or lobectomy versus patients traditionally operated via thoracotomy lobectomy or treated with stereotactic ablative radiotherapy. The findings revealed that patients undergoing thoracoscopic lobectomy had similar overall, cancer specific, and disease-free survival compared with patients undergoing thoracotomy lobectomy and that thoracoscopic techniques did not seem to compromise these measures of outcome after lobectomy. Even when compared to stereotactic ablative radiotherapy, the results suggested that the patients undergoing thoracoscopic surgical resection or lobectomy, particularly when the tumor sizes were large, might have improved cancer-specific survival compared with patients undergoing stereotactic ablative radiotherapy.[65, 66]

"Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database"

"Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population-based study with propensity matched comparative analysis"

Topic: Intermediate-term outcomes after robotic-assisted surgery vs. open radical surgery

Robot-assisted surgery has been rapidly adopted in the U.S. for several kinds of operations. Using the SEER-Medicare database, several studies compared the outcomes, healthcare costs and overall survival at mid-term of robotic-assisted cystectomy, prostatectomy, nephrectomy versus open radical surgery. The studies demonstrated that the robotic-assisted surgical procedures had similar

[65] Paul S, Isaacs AJ, Treasure T, Altorki NK, Sedrakyan A. Long term survival with thoracoscopic versus open lobectomy: propensity matched comparative analysis using SEER-Medicare database. *Bmj*. 2014;349:g5575.
[66] Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. Ibid.2016;354:i3570.

perioperative and survival outcomes and disease control, while the healthcare costs of robotic-assisted surgeries were found to be higher for cystectomy and prostatectomy, but not for nephrectomy.[67,68,69,70]

- ***"Perioperative Outcomes, Health Care Costs, and Survival After Robotic-assisted Versus Open Radical Cystectomy: A National Comparative Effectiveness Study"***
- ***"Comparative Effectiveness of Cancer Control and Survival after Robot-Assisted versus Open Radical Prostatectomy"***
- ***"Adoption of Technology and Its Impact on Nephrectomy Outcomes, a U.S. Population-Based Analysis (2008-2012)"***
- ***"Minimally invasive vs open nephrectomy in the modern era: does approach matter?"***

CRN-specific data sources

VASCULAR IMPLANT SURVEILLANCE & INTERVENTIONAL OUTCOMES NETWORK (VISION) DATA

VISION coordinated registry network (CRN) builds on the Vascular Quality Initiative (VQI) Registry and advances the maturation of the registry by the development of CRN via linkages to other data sources. The VQI, established by the Society for Vascular Surgery, is an Agency for Healthcare Research and Quality (AHRQ)-listed Patient Safety Organization (PSO) consisting of regional groups of physicians, data managers, and quality assurance professionals who collect data on vascular procedures to improve patient care. The VQI has more than 600 participating s centers across the United States and Canada. Initial work undertaken by the VQI-VISION team includes the creation of linked data sets for endovascular aneurysm repair, open abdominal aortic aneurysm repair, peripheral vascular interventions, thoracic endovascular aneurysm repair, carotid artery stenting, carotid endarterectomy, infra-inguinal bypass, supra-inguinal bypass hemodialysis access, and varicose vein procedures.

[67] Hu JC, Chughtai B, O'Malley P, et al. Perioperative Outcomes, Health Care Costs, and Survival After Robotic-assisted Versus Open Radical Cystectomy: A National Comparative Effectiveness Study. *Eur Urol.* 2016;70(1):195-202.
[68] Hu JC, O'Malley P, Chughtai B, et al. Comparative Effectiveness of Cancer Control and Survival after Robot-Assisted versus Open Radical Prostatectomy. *J Urol.* 2017;197(1):115-121.
[69] Golombos DM, Chughtai B, Trinh QD, et al. Minimally invasive vs open nephrectomy in the modern era: does approach matter? *World J Urol.* 2017;35(10):1557-1568.
[70] Golombos DM, Chughtai B, Trinh QD, et al. Adoption of Technology and Its Impact on Nephrectomy Outcomes, a U.S. Population-Based Analysis (2008-2012). *J Endourol.* 2017;31(1):91-99.

The VQI registry contains patient demographics (e.g., age, sex, race, and ethnicity), general health status (e.g., BMI, smoking status, ambulation), comorbidities at baseline, granular disease, vascular procedure, and device characteristics. The VQI started collecting device data from October 2016 with linkage to the Global Universal Device Identifier (GUDID). The VQI collects in-hospital complications and mortality, and patient discharge status. One to two-year follow-ups are also collected with varying completeness across different disease modules.

The VQI-Medicare linked data leverages baseline and short-term data from the VQI registry and long-term follow-up from Medicare claims data. Data include VQI patients with fee-for-service Medicare insurance. Deaths, readmissions, reinterventions, imaging surveillance use, and other major events (e.g., aneurysm rupture, stroke, amputation) following the index procedure can be identified using procedure and diagnosis codes in Medicare inpatient, outpatient, and carrier claims and master beneficiary summary file. The VQI has also been linked to statewide administrative data (e.g., New York State Statewide Planning and Research Cooperative System). VQI patients of all age groups in the specific state, regardless of the expected payer, are included in the linked data. Short and long-term outcomes, such as readmissions and reinterventions, following the index procedure can be identified from the state administrative data. Linked data can be used to examine long-term outcomes of a device-based vascular procedure, specific devices, and certain device attributes (see our published studies below).

Topic: EVAR reintervention in VQI-Medicare database:

The Society for Vascular Surgery's Vascular Quality Initiative (VQI) is an important tool in achieving complete long-term postoperative outcome data in vascular surgery. However, VQI data linkage to Medicare claims through indirect identifiers allows for a more comprehensive capture of major clinical outcomes after vascular procedures. Once the linkage algorithms between the two databases were refined, the combined VQI-Medicare database was used to define the 5-year rate of reintervention and rupture post endovascular abdominal aortic aneurysm repair

(EVAR).[71] [72]It was found that late rupture is low, and that African American patients, those with large aneurysms, and those who undergo EVAR urgently and emergently have a higher likelihood of adverse outcomes. Lastly, the rate of reintervention seemed to be similar between older, Medicare-eligible individuals, and those who are not yet eligible (patients that are younger than 65 years of age or with Medicare Advantage plans).[73]

"A pilot study for long-term outcome assessment after aortic aneurysm repair using Vascular Quality Initiative data matched to Medicare claims"

"Five-year reintervention after endovascular abdominal aortic aneurysm repair in the Vascular Quality Initiative"

"Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients"

Topic: Long-term outcomes of peripheral vascular interventions:

The VQI-Medicare database was also queried to investigate the long-term effectiveness of atherectomy for treatment of peripheral arterial disease. Three different types of surgeries were considered for this analysis: atherectomy, or percutaneous transluminal angioplasty (PTA). The effectiveness outcome measures considered were major amputation, any amputation, and major adverse limb event (major amputation or any reintervention). The findings concluded that the 5-year rate of major adverse limb events was 38% in patients receiving atherectomy versus 33% for PTA and 32% for stenting; atherectomy patients had similar outcomes as PTA patients, except for having an increased risk of all amputation types, while atherectomy patients had higher risk than stent patients of major amputation.[74]

[71] Hoel AW, Faerber AE, Moore KO, et al. A pilot study for long-term outcome assessment after aortic aneurysm repair using Vascular Quality Initiative data matched to Medicare claims. *Journal of vascular surgery*. 2017;66:751-759.e751.
[72] Columbo JA, Ramkumar N, Martinez-Camblor P, et al. Five-year reintervention after endovascular abdominal aortic aneurysm repair in the Vascular Quality Initiative. *J Vasc Surg*. 2020;71(3):799-805.e791.
[73] Columbo JA, Sedrakyan A, Mao J, et al. Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients. Ibid.2019;70:741-747.
[74] Ramkumar N, Martinez-Camblor P, Columbo JA, Osborne NH, Goodney PP, O'Malley AJ. Adverse Events After Atherectomy: Analyzing Long-Term Outcomes of Endovascular Lower Extremity Revascularization Techniques. *Journal of the American Heart Association*. 2019;8:e012081.

"Adverse Events After Atherectomy: Analyzing Long-Term Outcomes of Endovascular Lower Extremity Revascularization Techniques"

REGULATORY HIGHLIGHTS

VISION CRN has advanced the infrastructure suited to study utilization, longitudinal patients' outcomes and performance of medical devices at the device level. Following the series of validation studies, the linkage between VQI and Medicare claims was accomplished achieving up to 15 years of follow up advancing the capacity to study postmarket questions in vascular space.

ABDOMINAL CORE HEALTH CRN DATA

The abdominal core health CRN is a partnership between the Abdominal Core Health Quality Collaborative (ACHQC) and MDEpiNet. The ACHQC was established in 2013 as a national quality improvement initiative. Surgeons in private practice and academic settings created the registry to maximize the quality and value of hernia patient care. As of March 2022, the registry contains over 93,000 adults undergoing primary or recurrent ventral or inguinal repair from over 400 surgeons at 358 academics, private, or private with academic affiliation medical centers across the United States.

The ACHQC registry contains demographic, pre-operative, operative, 30-day follow-up, long-term follow-up, and patient-reported outcomes data for patients 18 years of age or older. The registry collects detailed real-world information on hernia-related medical devices and techniques used to treat hernia disease.

The ACHQC registry has been linked to New York State SPARCS data. Patients undergoing ventral hernia in New York State, regardless of age and expected payer, are included in the linkage. Short and long-term outcomes, including readmissions and reinterventions following the index procedure, can be identified from the state administrative data. The linkage between the ACHQC registry and Medicare claims is ongoing. Fee-for-service Medicare patients in the ACHQC are included in the linkage. Follow-up events that can be identified from Medicare claims include readmission, reintervention, and major complications.

Recent demonstration of the value created by the ACHQC for evaluation and surveillance of hernia-related medical devices suggests that investment in the registry might improve evidence generation about current and future devices and procedures, including enabling better faster and less costly recalls (manuscript under JAMA review). Future directions based on this work include harmonization of registry data collection and outcomes on an international scale.

REGULATORY HIGHLIGHTS

Efforts to link ACHQC data with State databases such as New York SPARCS, have advanced the capacity to study long-term safety and effectiveness of devices used for ventral hernia repair. In addition, we demonstrated that using registry infrastructure can lead to faster and less costly recalls nationally and internationally.

WOMEN'S HEALTH TECHNOLOGY CRN (WHT-CRN) DATA

To maximize the impact of the identified core data elements (CDE), a system that collects the CDE broadly within the workflow of surgeons performing surgeries may be helpful. Capturing the elements in a clinical setting at the point of care through electronic health records (EHR) negates the need for a separate data collection system such as a clinical trial or an independent post-market registry.[75] Operative forms are an option for inserting CDE into workflow.

A clinical area where the routine capture of CDE is pivotal for the efficient national post-market data collection is among uterine fibroid related treatment. Approximately 1 in 4 women will suffer from uterine fibroids within their lifetime.[76] Despite the high prevalence of the condition, there is a paucity of evidence evaluating the safety and effectiveness of these treatment options.[77] The effects of the limited available evidence related to the safety of some of these procedures and

[75] U.S. Department of Health and Human Services Food and Drug, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Use of Electronic Health Record Data in Clinical Investigations - Guidance for Industry*.

[76] U.S. Department of Health and Human Services - Office on Women's Health. Uterine Fibroids. Accessed 7 October 2019. https://www.womenshealth.gov/a-z-topics/uterine-fibroids

[77] Hartmann KE, Fonnesbeck C, Surawicz T, et al. *Management of Uterine Fibroids*.; 2017. https://www.ncbi.nlm.nih.gov/books/NBK537742/

devices were highlighted by the safety communications published by the United States (US) Food and Drug Administration (FDA).[78, 79] Given the regulatory history of some fibroid devices, efficient national post-market data collection could capture the real-time use and effects of important uterine fibroid devices. This type of national surveillance system with extractable data that can be mobilized to inform regulatory-, clinical-, and training-related decision-making may be useful in the context of devices where their safety or effectiveness may be called into question. Efforts, such as the Women's Health Technology Coordinated Registry Network (WHT-CRN), aim to address the existing data limitations and put in place the infrastructure needed for a comprehensive national surveillance system.[80] For these reasons, the WHT-CRN convened a group of stakeholders and, using the Delphi Method, established a core minimum dataset to capture the relevant data elements needed for the comprehensive evaluation of uterine fibroid treatments. The established CDE capture the needed data to inform patient-, clinical-, and regulatory-decision making. These elements encompass patient demographics, data related to the patient's medical history, imaging data, procedural data, post-procedural data, and long-term follow-up data.[81]

Operative forms could capture the real-time use and effects of important uterine fibroid devices. Currently, surgeons may complete a post-operative report after a fibroid surgery for documentation purposes and may insert many of the identified needed information in a free-text form.[82, 83] The data, however, is not efficiently extractable in this form. Integrating the needed data in an extractable form within existing mandatory operative forms could allow for the highly efficient and cost-effective data collection on all surgical cases, not just participants in a clinical study.

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[78] U.S. Food and Drug Administration. Laparoscopic Uterine Power Morcellation in Hysterectomy and Myomectomy: FDA Safety Communication.

[79] U.S. Food and Drug Administration. FDA Updated Assessment of The Use of Laparoscopic Power Morcellators to Treat Uterine Fibroids. Published 2017. Accessed 6 October 2019. https://www.fda.gov/media/109018/download

[80] Krucoff MW, Sedrakyan A, Normand S-LT. Bridging Unmet Medical Device Ecosystem Needs With Strategically Coordinated Registries Networks. *JAMA*. 2015;314(16):1691-1692. doi:10.1001/jama.2015.11036

[81] Medical Devices Epidemiology Network (MDEpiNet), U.S. Food and Drug Administration. *The Women's Health Technology Coordinated Registry Network (WHT-CRN).*; 2019.

[82] Katzan I, Speck M, Dopler C, et al. The Knowledge Program: an innovative, comprehensive electronic data capture system and warehouse. In: *AMIA Annual Symposium Proceedings*. Vol 2011. American Medical Informatics Association; 2011:683.

[83] Ehrenstein V, Kharrazi H, Lehmann H, Taylor CO. Obtaining Data From Electronic Health Records. In: *Tools and Technologies for Registry Interoperability, Registries for Evaluating Patient Outcomes: A User's Guide, 3rd Edition, Addendum 2 [Internet]*. Agency for Healthcare Research and Quality (US); 2019.

Presenting this type of form as an option to surgeons completing a post-operative report integrates the collection of desired data into a standardized operative note. Additionally, this approach allows for the eventual links to other critical data elements in electronic health records (EHRs), such as device identifiers. The objective of the present study was, thus, to integrate the uterine fibroid-specific CDE variables identified by the stakeholders within the WHT-CRN into the EPIC Electronic Health Record (EHR) in a way that variables can efficiently be extracted for data analyses and create a workflow process in which the CDEs are collected on patients undergoing fibroid surgery within sites utilizing the EPIC EHR system.

The integration of the identified CDE into EHR was performed using a multi-step process including (1) the review of existing operative reports, (2) the design of a uterine fibroid specific operative report, (3) the engagement of surgeons for the revision of the developed operative report, and (4) the integration and implementation of the operative report into the EHR system. More specifically, the first step included identifying the existing EPIC Operative Reports used at the University of California San Francisco (UCSF) institution and aggregating the identified reports. The UCSF team worked closely with the institution-specific EPIC research support group, to create an EPIC operative form that includes the CDE operative variables. Finally, the UCSF team partnered with high-volume surgeons to draft several versions of the operative report with different approaches to data collection and pilot tested the form among high-volume surgeons.

Out of the 39 procedure-related variables identified, only one variable was present in the existing operative form in a discrete and extractable form within the UCSF system. Feedback from high-volume surgeons resulted in several draft versions of the Operative Form with different approaches to data collection. Surgeon-provided user feedback specifically focused on dropdown menus, smart phrases, clickable boxes, and other methods to meet the aim of implementing the CDEs into the operative workflow. Additionally, the surgeons proposed five additional discrete data variables related to (1) the uterine size in weeks, (2) presence of adhesions, (3) presence of endometriosis, (4) presence of suspected cancer, and (5) any other abnormal or unanticipated findings. These variables were integrated into the final version of the operative form. The finalized operative form was implemented into the

EPIC EHR system in October 2020. The form displays the respective relevant field following the selection of the performed fibroid surgery and employed surgical route. The displayed fields include several discrete data collection fields and space for each physician to customize based on their individual preferences. This ensures that the final form is flexible, can adapt to different surgical preferences, and collect consistent, standardized data for the CDE fields.

The demonstrated feasibility of the successful integration of data elements into an EHR system within the women's health space is useful given the growing focus on EHRs by federal legislation as a means to improve quality of care and the management of conditions.[84,85] Moreover, the role of EHR in population-related research[86] and as a tool to capture and generate real-world evidence continues to expand.[11,87,88] Direct data extraction from EHRs at the point of care is also favorable since EHR present a source of continuous data flow, reduce the need for secondary data collection, and may minimize bias within studies that would otherwise rely on self-reporting.[89] This further ensures that any further datasets linked to the EHRs can also be fully leverage for research purposes,[9] and may reduce the need to harmonize or integrate multiple data sources after the fact. The finalized developed form is being implemented among all surgeons within the UCSF system for general use. This will allow for automated reports to be generated from the new form that can regularly provide all data on CDE variables to various stakeholders. The platform is ready to be shared and scaled across all users of the same EHR system. The data extracted may be used to create local and national standardized reports for quality improvement, develop teaching metrics, and provide data for research projects that inform clinical and regulatory decision making.

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[84] Blumenthal D, Tavenner M. The "meaningful use" regulation for electronic health records. *N Engl J Med*. 2010;363(6):501-504.

[85] Cowie MR, Blomster JI, Curtis LH, et al. Electronic health records to facilitate clinical research. *Clin Res Cardiol*. 2017;106(1):1-9. doi:10.1007/s00392-016-1025-6

[86] Casey JA, Schwartz BS, Stewart WF, Adler NE. Using Electronic Health Records for Population Health Research: A Review of Methods and Applications. *Annu Rev Public Health*. 2016;37:61-81. doi:10.1146/annurev-publhealth-032315-021353

[87] Selby J V, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. *Jama*. 2012;307(15):1583-1584.

[88] Deans KJ, Sabihi S, Forrest CB. Learning health systems. *Semin Pediatr Surg*. 2018;27(6):375-378. doi:10.1053/j.sempedsurg.2018.10.005

[89] Scholte M, van Dulmen SA, Neeleman-Van der Steen CWM, van der Wees PJ, Nijhuis-van der Sanden MWG, Braspenning J. Data extraction from electronic health records (EHRs) for quality measurement of the physical therapy process: comparison between EHR data and survey data. *BMC Med Inform Decis Mak*. 2016;16(1):141. doi:10.1186/s12911-016-0382-4

Papers published on the MDEpiNet website describing linked data sets for 5 most mature CRNs that can be used for multiple scientific analyses/studies.

INDIRECT LINKAGES

One of the main MDEpiNet methodological advancements has been to conduct linkages between registry data and routinely available data sources (e.g., claims and administrative data). We successfully developed and refined linkage algorithms to augment the research capacities of CRNs by bringing together registries, claims data, and EHRs. Data linkages with indirect identifiers are reliable, impart high sensitivity and accuracy, and provide positive implications for long-term device surveillance. This method is the most cost-effective way to obtain long-term outcomes. Below, we highlight the linkages we have completed in the fields of orthopedics, abdominal core health, and within the VISION CRN (peripheral artery, endovascular aneurysm repair, and carotid devices registries) using this method.

Ortho CRN: Creation and Validation of Linkage Between Orthopedic Registry and Administrative Data Using Indirect Identifiers

Data sources used: SPARCS, AJRR

Given the respective benefits of both registries and administrative databases in epidemiological research, the study sought to create an algorithm using indirect identifiers to link data from the American Joint Replacement Registry (AJRR) with SPARCS.[90] The study included hip and knee arthroplasty operations at six New York State hospitals enrolled in AJRR in 2014. A direct linkage was performed using patient identifiers such as social security numbers and names, which was then leveraged to validate an indirect method of linkage relying on facility ID, patients' year and month of birth, sex, zip code, and procedure date and site (hip/knee). The effect of indirect identifiers and compromised data quality on linkage success was also analyzed. The sequential algorithm produced a matching rate of

[90] Mao J, Etkin CD, Lewallen DG, Sedrakyan A. Creation and Validation of Linkage Between Orthopedic Registry and Administrative Data Using Indirect Identifiers. *J Arthroplasty.* 2019;34(6):1076-1081.e1070.

92.03% (3739 of the 4063), with an accuracy of >99.9%. These results were robust when one of the indirect identifiers was not available (90% sensitivity and 99.8% accuracy). This demonstrates the high sensitivity and accuracy of the proposed approach for creating linkages between registries and databases, a significant finding for long-term surveillance and outcome assessment of devices and procedures.

ACH CRN: Feasibility of linking registry data to administrative data for follow up after ventral hernia repair (VHR) using indirect patient identifiers

Data sources: ACHQC and SPARCS

A total of 503 New York State adults were identified in the ACHQC registry having ventral hernia procedures from 2014-2018. Of these, 433 (86.1%) of patients were successfully linked between the ACHQC registry and SPARCS data using 9 sequential steps. Long-term follow-up increased from 66.4 +/- 164.9 (mean +/- sd) days to 340.2 +/- 407.3 days, demonstrating the feasibility of supplementing long-term follow-up in ventral hernia repair using indirect identifiers. Indirect linkage was performed using a validated sequential matching algorithm as described by Mao (2019)[8] using the following indirect identifiers: date of surgery, month and year of birth, gender, and zip code. Manuscript is in submission.

VISION CRN:

VISION CRN consists of various registry databases as a result of data linkages to specific datasets including the overall database of the VQI/VISION registry, and more specific clinical areas such as the VQI/ Lower Extremities Registry (PVI, Supringuinal bypass and Infrainguinal bypass), VQI/EVAR, VQI/TEVAR, and VQI/ Carotid registries. Below, we describe the registry linkages with claims, Medicare, and EHRs.

VQI/VISION Registry

1. Validation of an indirect linkage algorithm to combine registry data with Medicare claims[91]

Data sources used: VQI, Medicare

[91] Mao J, Moore KO, Columbo JA, Mehta KS, Goodney PP, Sedrakyan A. Validation of an indirect linkage algorithm to combine registry data with Medicare claims. J Vasc Surg. 2022 Jul;76(1):266-271.e2. doi: 10.1016/j.jvs.2022.01.132. Epub 2022 Feb 15. PMID: 35181518; PMCID: PMC9443721.

In this study, we developed and validated a data linkage algorithm between registries and Medicare claims that does not rely on patient identifiers, thus extending follow-up for patients receiving medical devices.[92] Data were drawn from the Vascular Quality Initiative (VQI), and further restricted to patients 65 and older who had a fee-for-service entitlement at the time of procedure. An indirect linkage was performed using a sequential algorithm based on patient's date of birth, sex, zip code, procedure date, and procedure facility. This was compared against a gold standard generated from a cohort directly linked using social security numbers. Of 144,045 VQI-Medicare linked patients in the gold standard cohort, we matched 133,966 to their Medicare claims for an overall matching rate of 93.0%. Among these patients, 133,104 were correctly matched, with a of 99.4% accuracy. The matching rate was higher for ICD-10 coded data as compared to ICD-9 coded data, and remained high (overall 99.4%, range 99.0-99.7%) for procedure modules post-ICD-10. These results show success in indirectly linking Medicare claims and registries with over 90% success and over 99% accuracy. This presents a suitable alternative when a direct linkage is not possible to achieve.

2. *The Vascular Implant Surveillance and Interventional Outcomes (VISION) Coordinated Registry Network: An effort to advance evidence evaluation for vascular devices*[93]

Data sources used: VQI-Medicare

The linkage of VISION's VQI registries to Medicare, which has been previously described in this report, has facilitated efficient, cost-saving, and effective evidence generation and appraisal. This work has broad impact, advancing data collection, improving surveillance of long-term procedural outcomes, and furthering trial aims through the CRN structure. In the future,

[92] Mao J, Moore KO, Columbo JA, Mehta KS, Goodney PP, Sedrakyan A. Validation of an indirect linkage algorithm to combine registry data with Medicare claims. *J Vasc Surg*. 2022.

[93] Tsougranis G, Eldrup-Jorgensen J, Bertges D, Schermerhorn M, Morales P, Williams S, Bloss R, Simons J, Deery SE, Scali S, Roche-Nagle G, Mureebe L, Mell M, Malas M, Pullin B, Stone DH, Malone M, Beck AW, Wang G, Marinac-Dabic D, Sedrakyan A, Goodney PP. The Vascular Implant Surveillance and Interventional Outcomes (VISION) Coordinated Registry Network: An effort to advance evidence evaluation for vascular devices. J Vasc Surg. 2020 Dec;72(6):2153-2160. doi: 10.1016/j.jvs.2020.04.507. Epub 2020 May 20. PMID: 32442604.

VISION strives to validate long-term outcome data in the VQI using industry datasets, with the goal of using CRNs to make device regulatory decisions and improve vascular disease patient care. This progress will be guided by a steering committee composed of leaders from clinical practice, industry, and regulatory organizations.

3. *Manuscript under review*

Data sources used: VISION, VQI-Medicare

Despite clinical trials on implanted devices, follow-up and surveillance are limited and sometimes incomplete with regard to late failure, which can be remedied through Medicare claim linkages. This study matched clinical trial and Medicare claims-based registry data to compare long-term device outcomes for endovascular aortic aneurysm repair (EVAR) patients. More specifically, data was matched between industry-sponsored IDE trials and the Vascular Implant Surveillance and Interventional Outcomes Network (VISION) registry. Primary outcomes analyzed were survival and freedom from aneurysm-related reintervention. 115/134 eligible patients were successfully matched (or 159 total clinical trial patients). For the matched cohort, the Kaplan-Meier estimated survival was 94.8% at one year, 82.6% at three years, and 68.1% at five years. Estimates for freedom from reintervention were 90% at one year, 82.4% at three years, and 78.1% at five years. The estimates for survival were nearly identical between the clinical trial data and that found in the VISION data (log-rank p=0.89). Freedom from reintervention was similar between the groups, with IDE trial reported freedom from reintervention of 87.3% and 73.3%, compared to VISION of 92.6% and 83% at one and five years, respectively (log-rank p=0.13).

4. *Manuscript under review*

Data sources used: VQI- INSIGHT Clinical Data Research Network (CDRN)

Vascular registries and EHR data both present valuable benefits; this study aimed to assess the feasibility of a linkage between these sources. This

study linked VQI and the INSIGHT CDRN using an indirect linkage algorithm, previously validated to have 90% matching rate and >99% accuracy. Baseline characteristics of the linked cohort and the long-term follow-up enrollment of linked patients in EHR were assessed, accounting for death, as well as 90-day readmission and long-term major adverse limb events (MALE, a subsequent amputation or lower limb reintervention) after the initial PVI procedure using Kaplan Meier analyses (censoring at the end of enrollment or death, whichever was earlier). The study identified 5,115 eligible patients from VQI, of which 88.2% were linked to the EHR, among whom, 432 underwent a PVI procedure with balloon angioplasty, stenting, atherectomy, or a combination of them and were included in the final cohort. After censoring for death, patient enrollment at 2 years was 46% at 2 years and 10% at 5 years, while cumulative incidence of readmission was 18.5% at 30 days and 36.2% at 90 days. Cumulative incidence of MALE at 2 years was found to be 46% and 57.5% at 5 years. This study demonstrates the feasibility of clinical registry and EHR data linkage.

VQI/ Lower Extremities Registry

1. Analyzing Long-Term Outcomes of Endovascular Lower Extremity Revascularization Techniques[94]

Data sources: VQI-Medicare claims

This publication was previously discussed in the context of long-term outcomes of peripheral vascular interventions. Here, we will discuss the data linkage aspect utilized in this study. We queried the Medicare-linked VQI registry for three types of endovascular interventions (atherectomy (with or without percutaneous transluminal angioplasty [PTA]), stent (with or without PTA), or PTA alone) from 2010 to 2015 with three outcomes (major amputation, any amputation, and major adverse limb event- major amputation or any reintervention). We concluded that after controlling for unmeasured confounding using instrumental-variable analysis, patients

[94] Ramkumar N, Martinez-Camblor P, Columbo JA, Osborne NH, Goodney PP, O'Malley AJ. Adverse Events After Atherectomy: Analyzing Long-Term Outcomes of Endovascular Lower Extremity Revascularization Techniques. *Journal of the American Heart Association.* 2019;8:e012081.

treated with atherectomy experienced outcomes similar to those of patients treated with PTA, except for a higher risk of any amputation. However, compared with stenting, atherectomy patients had a higher risk of major amputation, any amputation, and major adverse limb event.

2. *Real-world study of mortality after the Use of Paclitaxel-coated Devices in Peripheral Vascular Intervention*[95]

Data sources: VQI -Medicare

We included patients undergoing percutaneous transluminal angioplasty and/or stent placement during 1/10/2015-31/12/2018 in the Vascular Quality Initiative Registry linked to Medicare claims. We determined differences in patient mortality and ipsilateral major amputation after PVI with PCD and non-PCD using Kaplan-Meier analyses and Cox regressions with inverse probability weighting in three cohorts: (A) patients treated for femoropopliteal or infrapopliteal occlusive disease with/without any other concurrent treatment (n=11 452), (B) those treated for isolated superficial-femoral or popliteal artery disease (n=5 519), and (C) patients with inclusion criteria designed to approximate RCT populations (n=2 278).

The mean age of patients was 72.3 (SD=10.9) years, and 40.6% were female. In cohort A, patients receiving PCD had lower mortality (HR 0.88, 95% CI 0.79-0.98) than those receiving non-PCD. There was no significant difference in mortality between groups in cohort B (HR 0.91, 95% CI 0.80-1.04) and C (HR 1.10, 95% CI 0.84-1.43). Patients receiving PCD did not have a significantly elevated risk of major amputation compared with those receiving non-PCD (Cohort A: HR=0.84, 95% CI 0.70-1.00; B: HR=0.84, 95% CI 0.67-1.06; C: HR=1.05, 95% CI 0.51-2.14).

We did not find increased patient mortality or major amputation at three years after PVI with PCD vs. non-PCD in this large, linked registry-claims

[95] Mao J, Sedrakyan A, Goodney PP, Malone M, Cavanaugh KJ, Marinac-Dabic D, Eldrup-Jorgensen J, Bertges DJ. Real-world study of mortality after the Use of Paclitaxel-coated Devices in Peripheral Vascular Intervention. Eur J Vasc Endovasc Surg. 2022 Aug 22:S1078-5884(22)00520-2. doi: 10.1016/j.ejvs.2022.08.014. Epub ahead of print. PMID: 36007713.

study, after accounting for heterogeneity of treatment effect by population. Our analysis and results from three cohorts intended to mirror the cohorts of prior studies provide robust and niche real-world evidence on PCD safety and help understand and reconcile previously discrepant findings.

3. *Validation of an indirect linkage algorithm to combine registry data with Medicare claims.*[96]

Data sources: VQI + Medicare claims

We compared the indirectly linked cohort against a reference standard of a cohort directly linked using Social Security numbers. We calculated the matching rate and accuracy overall and before and after October 2015 when the International Classification of Diseases, 10th revision (ICD-10) system was adopted in the United States.

A total of 144,045 VQI-Medicare-linked patients were in the reference standard cohort. Using the indirect linking algorithm, we matched 133,966 of the 144,045 VQI patients to their Medicare claims with a matching rate of 93.0%. Of the 133,966 patients, 133,104 were correctly matched (matching accuracy, 99.4%). The matching rate was higher when the indirect linkage was implemented using the ICD-10 coded data than using the ICD-9 coded data (94.0% vs 92.2%). The accuracy of the indirect linkage remained high for all procedure modules after the ICD-10 coding change (overall, 99.4%; range, 99.0%-99.7%).

When direct linkage of the registry claims data using Social Security numbers is not possible because of availability or confidentiality, or both, our algorithm for indirect linkage provides a suitable alternative. The matching rate and accuracy will help ensure the accuracy of long-term follow-up and the completeness and representativeness of linked databases for relevant research and quality improvement initiatives.

[96] Mao J, Moore KO, Columbo JA, Mehta KS, Goodney PP, Sedrakyan A. Validation of an indirect linkage algorithm to combine registry data with Medicare claims. J Vasc Surg. 2022 Jul;76(1):266-271.e2. doi: 10.1016/j.jvs.2022.01.132. Epub 2022 Feb 15. PMID: 35181518; PMCID: PMC9443721.

VQI/ EVAR Registry

1. *Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients* [97]

Data sources: VQI and SPARCS

Patients in the VQI registry who underwent endovascular aortic aneurysm repair (EVR) between 2011-2015 were linked in SPARCS at the patient level with a 96% match rate, and the outcomes were then compared against fee-for-service Medicare eligibility requirements, as defined by age and dialysis status. The primary outcome was reintervention. The study revealed that the rate of reintervention is similar between older, Medicare eligible individuals and those who are not yet eligible, in both the adjusted analysis and in our Cox proportional hazards regression and propensity score matching analysis.

2. *Late outcomes after endovascular and open repair of large abdominal aortic aneurysms* [98]

Data sources: EVAR and VQI-Medicare

The risk of aortic abdominal aneurysm (AAA) rupture increases with an increasing aneurysm diameter. However, the effect of the AAA diameter on late outcomes after aneurysm repair is unclear. Therefore, in this study we assessed the association between a large AAA diameter with late outcomes for patients undergoing open and endovascular AAA repair. The 5-year reintervention, rupture, mortality, and follow-up rates was assessed in all patients in the VQI registry who underwent elective open or endovascular infrarenal aneurysm repair between 2003 and 2016. We found that after EVAR, patients with large AAAs had had lower adjusted 5-year freedom from reintervention, freedom from rupture, survival, and freedom from loss to follow-up compared with patients with smaller AAAs. However, after open repair, the adjusted 5-year freedom from reintervention, rupture, survival, and loss to follow-up were similar to the results for patients with smaller AAAs. Therefore, for patients with large AAAs who are medically fit, open repair should be strongly considered.

Three open access analyses codes and implementations guides (posted on the MDEpiNet website) for: 1) Machine learning methodologies applied to CRN linked datasets to derive causal inference; 2) Augmentation approaches to obtain missing data in the CRN big data settings; 3) Transporting the results to specific CRN target populations to enable exact matching;

Use of Machine Learning Methods

Regulatory bodies, clinicians and PCOR researchers have increasingly accepted and leveraged the use of real word evidence (RWE) generated from real-world data (RWD) to inform regulatory and clinical decision making.[99, 100, 101] RWD can not only be used to retrospectively assess the effectiveness and safety of revascularization procedures but can also be used to formulate models that help determine risk factors and probabilities of successful revascularization among patients needing percutaneous treatment.. Predictive models can be generated using traditional regression-based techniques or machine-learning techniques.

Machine learning models may overcome a number of limitations associated with traditional regression-based models and therefore, be more suitable for high-quality and high-dimensional data.[102, 103] Machine learning predictive models have previously been developed within the cardiovascular space to predict readmissions and bleeding.[104, 105] It may thus be possible to expand

[97] Columbo JA, Sedrakyan A, Mao J, et al. Claims-based surveillance for reintervention after endovascular aneurysm repair among non-Medicare patients. *J Vasc Surg*. 2019;70(3):741-747.

[98] de Guerre L, Dansey K, Li C, et al. Late outcomes after endovascular and open repair of large abdominal aortic aneurysms. Ibid.2021;74(4):1152-1160.

[99] Cronenwett JL, Avila-Tang E, Beck AW, et al. Use of data from the Vascular Quality Initiative registry to support regulatory decisions yielded a high return on investment. *BMJ Surgery, Interv & Heal Technol*. 2020;2(1):e000039. doi:10.1136/bmjsit-2020-000039

[100] U.S. Department of Health and Human Services - Food and Drug Administration: Center for Devices and Radiological Health and Center for Biologics Evaluation and Research. *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices - Guidance for Industry and Food and Drug Administration Staff.*; 2017. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidance

[101] U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. Published online 2018:1-37. doi:10.1038/sj.bdj.2012.1047

[102] Goldstein BA, Navar AM, Carter RE. Moving beyond regression techniques in cardiovascular risk prediction: applying machine learning to address analytic challenges. *Eur Heart J*. 2016;38(23):1805-1814. doi:10.1093/eurheartj/ehw302

[103] Doupe P, Faghmous J, Basu S. Machine Learning for Health Services Researchers. *Value Heal*. 2019;22(7):808-815. doi:https://doi.org/10.1016/j.jval.2019.02.012

[104] Zack CJ, Senecal C, Kinar Y, et al. Leveraging Machine Learning Techniques to Forecast Patient Prognosis After Percutaneous Coronary Intervention. *JACC Cardiovasc Interv*. 2019;12(14):1304-1311. doi:https://doi.org/10.1016/j.jcin.2019.02.035

[105] Mortazavi BJ, Bucholz EM, Desai NR, et al. Comparison of Machine Learning Methods With National Cardiovascular Data Registry Models for Prediction of Risk of Bleeding After Percutaneous Coronary Intervention. *JAMA Netw open*. 2019;2(7):e196835. doi:10.1001/jamanetworkopen.2019.6835

predictive modeling capabilities into vasculature conditions of the lower limbs. The vascular space has the advantage of having a mature national registry, known as the Vascular Quality Initiative (VQI). The VQI captures a range of patients with vascular disease and documents in-depth information regarding the patient, indication, and procedure characteristics not captured in claims databases. Registries are an important source of RWD and have been continuously used to inform clinical and regulatory decision making.[16, 106] Thus far, the VQI registry has primarily been used to evaluate the safety and effectiveness of vascular treatments.[107, 108] Given its capabilities and dimensionality, the VQI registry can further be leveraged, and its use expanded beyond the assessment of safety and effectiveness to include predictive modeling. Robust predictive models allow for the determination of the role factors related to the patient, indication, devices, and procedures play in the unsuccessful revascularization among patients diagnosed with PAD. The objective of our study was to formulate and test a model used to predict major adverse limb events (MALE) and mortality among patients receiving treatment for lower extremity PAD.

Patients undergoing atherectomy, stenting, and combination stenting and atherectomy for lower extremity peripheral artery disease were identified in the Vascular Quality Initiative registry. Thirty-nine variables summarizing demographic, medical history, pre-operative, indication-specific, and procedure-specific characteristics were utilized to predict MALE and mortality events. For both events, we compared the performance of four different prediction models: a generalized linear model (GLM), a Least Absolute Shrinkage and Selection Operator (LASSO) regularized GLM, a gradient boosted decision tree, and random forest model. The area under the curve

[106] Tsougranis G, Eldrup-Jorgensen J, Bertges D, et al. The Vascular Implant Surveillance and Interventional Outcomes (VISION) Coordinated Registry Network: An Effort to Advance Evidence Evaluation for Vascular Devices. *J Vasc Surg*. Published online 2020. doi:https://doi.org/10.1016/j.jvs.2020.04.507

[107] Bertges DJ, White R, Cheng Y-C, et al. Registry Assessment of Peripheral Interventional Devices Objective Performance Goals for Superficial Femoral and Popliteal Artery Peripheral Vascular Interventions. *J Vasc Surg*. Published online November 17, 2020. doi:10.1016/j.jvs.2020.09.030

[108] Ramkumar N, Martinez-Camblor P, Columbo JA, Osborne NH, Goodney PP, O'Malley AJ. Adverse Events After Atherectomy: Analyzing Long-Term Outcomes of Endovascular Lower Extremity Revascularization Techniques. *J Am Heart Assoc*. 2019;8(12):e012081. doi:10.1161/JAHA.119.012081

(AUC) evaluated the effectiveness of each prediction model. For validation purposes, 5-fold cross-validation was repeated three times. Pairwise comparisons of the receiver operating characteristic curves (ROC), sensitivity, and specificity measures with Bonferroni adjustment for multiple testing applied were performed to compare the models' performance.

Among 15964 identified patients, a MALE occurred in 26.02% of patients, and death occurred in 18.82% of patients. The most effective predictive model for MALE, as determined by the AUC, was the gradient boosted decision tree (AUC= 0.7539) followed by the LASSO regulated GLM (AUC= 0.749). The GLM model (0.006;p<.020) and gradient boosted model (0.010;p<.039) produced a significantly higher ROC than the random forest model. The most effective predictive model for mortality was the LASSO regularized GLM (AUC=0.7930) followed by the GLM model (AUC=0.7922). The GLM, LASSO regularized GLM model, and gradient boosted decision tree produced similar ROC. The LASSO model (0.014; p<.008) produced a significantly higher ROC than the random forest model.

The identified leading predicting variables in all models were primarily related to PAD's risk factors and symptoms, commonly occurring comorbidities, and indication-specific characteristics. The identified leading predictors related to the symptomology of PAD included leg symptoms. Identified PAD risk factors included BMI category and age category. Identified medical conditions included diabetes, chronic kidney disease, and congestive heart failure.[109, 110, 111, 112] Identified indication-specific characteristics included the type of artery treated. Treatment type was only indicated as a leading predictor in one model, indicating that patient and procedure-related characteristics may play a more significant role in treatment outcomes than the treatment itself.

[109] Conte MS, Pomposelli FB, Clair DG, et al. Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities: management of asymptomatic disease and claudication. *J Vasc Surg*. 2015;61(3 Suppl):2S-41S. doi:10.1016/j.jvs.2014.12.009

[110] Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*. 1997;277(9):739-745.

[111] Ruff CT, Bhatt DL, Steg PG, et al. Long-term cardiovascular outcomes in patients with atrial fibrillation and atherothrombosis in the REACH Registry. *Int J Cardiol*. 2014;170(3):413-418. doi:10.1016/j.ijcard.2013.11.030

[112] Faulkner KW, House AK, Castleden WM. The effect of cessation of smoking on the accumulative survival rates of patients with symptomatic peripheral vascular disease. *Med J Aust*. 1983;1(5):217-219.

While all models showed acceptable discrimination, the machine learning models did not always perform significantly better in terms of AUC than more traditional regression-based baseline models.[113] All models had low specificity. The model performance may improve with more available predictors and a higher event rate. The models should be regenerated as more years of data are made available, and more events thus captured.[114] Leveraging linked datasets may further facilitate the capture of more events of interest. Linking to claims may provide further predictors by identifying more current medical conditions and prescription medications. Moreover, claims may help identify additional outcomes outside of the hospital systems reporting to the VQI.[115,116] The increased predictors and event rates may increase the discriminatory power of the model. Efforts, such as the Vascular Implant Surveillance and Interventional Outcomes Network (VISION) Coordinated Registry Network (CRN), may facilitate access to the longitudinal linked data sources needed to generate stronger predictive models.[23] This study supports the use of predictive modeling within the clinical space of lower extremity peripheral artery disease. Future machine learning models may employ additional data and linkage to other data sources to further inform and increase the generated predictive models' discriminatory ability.

Missing Data in Registry Studies (VQI)

The objective of this study was to evaluate the short- and long-term major adverse limb event (MALE) following the receipt of stenting, atherectomy, and the combination of stent and atherectomy. A retrospective cohort of patients undergoing atherectomy, stent, and combination stent atherectomy for lower extremity peripheral artery disease was derived from the Vascular Quality Initiative (VQI) dataset. The primary outcome was MALE and was assessed in

[113] Mandrekar JN. Receiver Operating Characteristic Curve in Diagnostic Test Assessment. *J Thorac Oncol*. 2010;5(9):1315-1316. doi:https://doi.org/10.1097/JTO.0b013e3181ec173d

[114] Junqué de Fortuny E, Martens D, Provost F. Predictive Modeling With Big Data: Is Bigger Really Better? *Big Data*. 2013;1(4):215-226. doi:10.1089/big.2013.0037

[115] Hoel AW, Faerber AE, Moore KO, et al. A pilot study for long-term outcome assessment after aortic aneurysm repair using Vascular Quality Initiative data matched to Medicare claims. *J Vasc Surg*. 2017;66(3):751-759.e1. doi:10.1016/j.jvs.2016.12.100

[116] Columbo JA, Kang R, Hoel AW, et al. A comparison of reintervention rates after endovascular aneurysm repair between the Vascular Quality Initiative registry, Medicare claims, and chart review. *J Vasc Surg*. 2019;69(1):74-79.e6. doi:10.1016/j.jvs.2018.03.423

the short-term and long-term. Short-term MALE was assessed immediately following the procedure to discharge and estimated using logistic regression. Prior to model specification, correlation matrices were created for all covariates to check for correlations greater than .85. Stepwise regression with forwards and backwards selection was utilized for model specification for short-term and long-term MALE.[117] A p-value of 0.10 is required for entry, and p-value of 0.05 is required to exit. For variables of interest with more than 60% of missing data, potential proxies were identified through cross-tabulation and correlation matrices. Patients with more than 8 variables of interest missing were removed from the analytic cohort. For variables of interest without high levels of missingness, multiple imputation by fully conditional specification was used to generate 20 datasets and impute multivariate missing data among all binary or categorical variables.[118,119,120] Logistic regression was used to calculate the risk of short-term MALE. The known competing risk of mortality must be accounted for when assessing the risk of long-term MALE.

Among the 46108 included patients, 6896 (14.95%) underwent atherectomy alone, 35774 (77.59%) received a stent, and 3438 (7.5%) underwent a combination of stenting and atherectomy. Within the VQI cases only 9 cases with complete data were identified. Thirty-eight individuals were removed because they had more than 8 variables containing missing data. The adjusted model indicated a significantly higher odds of short-term MALE in the atherectomy group (OR=1.34; 95%CI:1.16-1.56), and not significantly different odds (OR=0.94;95%CI:0.77-1.14) in the combination stent and atherectomy group when compared to stenting alone. With regards to long-term MALE, the model indicated that the likelihood of experiencing the outcome was slightly lower (HR=0.90; 95%CI:0.82-0.98) in the atherectomy

[117] Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3:17. doi:10.1186/1751-0473-3-17

[118] Course Hero. Alternative Method for Imputation is Fully Conditional Method. Accessed 21 June 2020. https://www.coursehero.com/file/p5btctfq/Alternative-method-for-imputation-is-Fully-Conditional-Method-FCS-FCS-does-not/

[119] UCLA Institute for Digital Research and Education. Multiple Imputation in SAS Part 1.

[120] Smith C, Kosten S. Multiple Imputation : A Statistical Programming Story. Published online 2017:1-16. https://www.pharmasug.org/proceedings/2017/SP/PharmaSUG-2017-SP01.pdf

group, and not significantly different (HR=0.92; 95%CI:0.82-1.04) in the combination stent and atherectomy group when compared to the stent group. Patients in the VQI dataset who received combination stenting and atherectomy did not experience significantly different rates of MALE when compared with stenting alone. These findings may indicate that the appropriate patient population received the combined treatment. Combined treatment may be warranted among these patients to ensure their risk of amputation is similar to those receiving stenting alone.

Missing Data among Medical Device Evaluations (SANEST)

The effect of missingness is of particular importance in the safety evaluation of paclitaxel coated devices. On December 2018, Katsanos et al., published a meta-analysis of long-term mortality rates in 28 randomized controlled trials (RCTs) and concluded that the risk of death was significantly greater in patients treated with drug-eluting devices than the control devices.[121] In June 2019, the Food and Drug Administration (FDA) convened a public advisory committee meeting to discuss late mortality signal and provide recommendations on the necessary regulatory actions.[122] The committee reviewed the existing evidence and noted that the studies thus far, including the meta-analysis, confirmed the mortality signal, though the data suffer from significant limitations, most notably data missingness. Two studies were performed to (1) illustrate the impact of methodological factors including missingness in data on the conclusions regarding the importance of methodological factors in the assessment of datasets for regulatory decisions such as the PTX example and (2) summarize the persistent issue of missing data, highlight how failing to properly account for missingness can result in unreliable inference, and provide guidelines on preventing, monitoring, assessing, and if needed, using statistical methods to account for the missingness.

[121] Katsanos K, Spiliopoulos S, Kitrou P, Krokidis M, Karnabatidis D. Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*. 2018;7(24):e011245. doi:10.1161/JAHA.118.011245

[122] U.S. Food and Drug Administration. June 19-20, 2019: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement. Published 2019. Accessed 25 July 2020. https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-19-20-2019-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting

It is known that missing data may lead to incorrect conclusions in clinical trials, especially in cases when they introduce systemic bias into the study.[123] The persistent issue of missing data, highlight how failing to properly account for missingness can result in unreliable inference, and provide guidelines on preventing, monitoring, assessing, and if needed, using statistical methods to account for the missingness, a systematic review of concepts covering 1) assessment of amount of missing data; 2) describing criticality of each variable; 3) investigating the type of and reason for missing data; 4) reviewing the possible methods of remediation based on type and amount was conducted. The findings emphasized that the assessment of the criticality of the variables is necessary to understanding its importance to accurate study results and interpretation. While data missing completely at random (MCAR) are less likely to result in bias, most data are missing with some non-randomness and can introduce bias, thereby requiring correction. Possible solutions include attempting to obtain the missing data by following up with study participants; excluding participants with missing variables from analyses, noting that doing so may introduce bias and reduce efficiency; or implementing statistical techniques post-hoc such as multiple imputation or maximum likelihood methods. Based on cause, type, amount and other characteristics of the missing data, sensitivity analyses are recommended to assess their potential impact. The late-mortality signal in paclitaxel-containing devices provides a motivational example of immediate relevance today and paramount to public health, for both preventing missing data and correctly handling and reporting missing data. Vigilance in follow-up, focus on retention, and a careful eye toward implications and interpretation of missing data brings missing data methods to the forefront.

[123] Little RJ, D'Agostino R, Cohen ML, et al. The Prevention and Treatment of Missing Data in Clinical Trials. *N Engl J Med*. 2012;367(14):1355-1360. doi:10.1056/NEJMsr1203730

Machine learning methods in medical device research using routinely available data sources.

Several large administrative data sources can be used for short and long-term evaluation of medical devices.[124,125,126] There is growing interest in using machine learning (ML) methods to improve the outcome risk prediction in medical device outcomes research. We implemented machine learning methods in three projects focusing on different medical devices. We used random forest (RF) models[127,128] to create predictive models of outcomes. RF is a nonparametric tree-based learning method of ML that is widely used for prediction or classification. Survival RF algorithms extend the tree-ensemble approach to the right-censored survival setting. RF can also examine importance of predictors using Gini index or mean decrease of accuracy.

In WHT CRN, we examined long-term outcomes after mesh-based sling device use in stress urinary incontinence using longitudinal discharge database in the New York State.[129] The RF was used to predict time to mesh erosion and time to reoperation, with demographic and clinical predictors. In this project, random forest analyses demonstrated poor prediction of outcomes (>40% error for each outcome). We further used the model to identify most important variables in predicting time to erosion and time to reoperation.

In cardiac CRN, we examined in-hospital mortality after using Extracorporeal membrane oxygenation (ECMO) using longitudinal discharge database in the New York State and National Inpatient Sample. RF algorithm performance was again poor, and the RF method was used to only determine three most important risk factors and their interactions. We created patient risk profiles based on all combinations of these risk factors and then used a random

[124] Chughtai B, Mao J, Matheny ME, Mauer E, Banerjee S, Sedrakyan A. Long-Term Safety with Sling Mesh Implants for Stress Incontinence. *J Urol*. 2021;205(1):183-190.
[125] Mao J, Pfeifer S, Schlegel P, Sedrakyan A. Safety and efficacy of hysteroscopic sterilization compared with laparoscopic sterilization: an observational cohort study. *Bmj*. 2015;351:h5162.
[126] Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. Ibid.2016;354:i3570.
[127] Breiman L. *Random forests. Machine learning. 2001,* . 2001.
[128] Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. *The Annals of Applied Statistics*. 2008;2(3):841-860, 820.
[129] Chughtai B, Mao J, Matheny ME, Mauer E, Banerjee S, Sedrakyan A. Long-Term Safety with Sling Mesh Implants for Stress Incontinence. *J Urol*. 2021;205(1):183-190.

forest regression model to obtain predicted mortality for each profile. This approach proved very useful for risk stratification and helped provide information that can be used for maximizing the outcomes of the device in emergency situations.

In a non-CRN proof-of-concept project, we examined long-term survival after resection or ablation of early-stage liver cancers using SEER-Medicare data. We determined the importance of risk factors for patients' overall survival using the survival random forest algorithm. Risk factors studied were procedure group, patient demographics (age, sex, race and ethnicity), year of procedure, residential population density, marital status, tumor size, socioeconomic status, comorbidities and comorbidity counts, liver disease prognostic indicators, and hospital procedure volume. Test error of the random forest model was still poor (between 30% to 35%).

In these three projects, important predictors identified by random forest were not necessarily variables that had the largest magnitude in terms of their effect measures (hazard ratios or odds ratios) when included in a regression model as an independent risk factor. The interpretation of the 'importance' was not very clear from a practical standpoint. In addition, the performance of machine learning models in these data sources was similar to that of regression models. However, predictors identified by machine learning models can be helpful for identifying risk profiles by accounting for interactions between the most important predictors as shown in the ECMO project.

The ML/RF can be helpful in risk prediction when using large database for device research. However, to achieve a full potential of these methods, one can conceive of combining them with regression methods into 'hybrid' approaches for more robust risk prediction and stratification.

Clustered bootstrap for standardization with

One aspect that needs to be considered in the CRN research is the presence of provider-level information. Clustered data by providers are often used in medical device research. Analysis using clustered data needs

machine learning in causal inference

to account for the similarities of patients within clusters[130]. Analysis without accounting for clusters may underestimate or overestimate the variance of the treatment coefficient (e.g., device coefficient). Standardization (also called G-formula or G-computation) is a causal inference method that estimates the average treatment effect by comparing the standardized mean in the treated and untreated.[131] It is an alternative method to regression, propensity score matching, and inverse probability weighting. Recently, standardization with machine learning methods has been implemented to perform comparative analysis and estimate the causal treatment effect.[132]

The first step of the research used simulated clustered datasets to assess the use of simple vs. clustered bootstrap with resampling in estimating variance and CIs of the device coefficient. We used 36 simulated datasets generated by a multi-step, hierarchical data generating process. The simulated data were patient-level data nested within provider clusters, with two device treatment groups (target vs. control). The 36 simulated datasets were designed to have four levels of clustering by operating surgeons, with the intraclass correlation (ICC) designed at 0 (no clustering effect), 0.1, 0.25, and 0.4 (9 datasets each). The prevalence of the target device was specified to be 0.1, 0.25, or 0.5. The prevalence of the outcome variable, adverse events, was specified to be 0.1, 0.25, or 0.5. The device effect was designed to an odds ratio (OR) of 1.5 in all datasets. Clustered bootstrap methods have been proposed to obtain robust estimators of the variance and confidence intervals (CI) of the treatment coefficient in multilevel regression models.[133] We sought to implement clustered bootstrap for standardization with machine learning methods in medical device research in the presence of hierarchical data.

[130] Feng Z, McLerran D, Grizzle J. A comparison of statistical methods for clustered data analysis with Gaussian error. Statistics in medicine. 1996 Aug 30;15(16):1793-806.
[131] Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC. 2020.
[132] Le Borgne F, Chatton A, Léger M, Lenain R, Foucher Y. G-computation and machine learning for estimating the causal effects of binary exposure statuses on binary outcomes. Scientific reports. 2021 Jan 14;11(1):1-2.
[133] Austin PC, Leckie G. Bootstrapped inference for variance parameters, measures of heterogeneity and random effects in multilevel logistic regression models. Journal of Statistical Computation and Simulation. 2020 Nov 21;90(17):3175-99.

Standardization with two machine learning methods was implemented: 1) Lasso logistic regression, and 2) feed-forward neural network model with one hidden layer. Two bootstrap methods with resampling were assessed: 1) simple bootstrap of individual-level data, and 2) two-stage stage clustered bootstrap by providers. We estimated the OR of adverse events comparing target vs. control devices and its CI using standardization with these two machine learning methods and simple and clustered bootstrap. For each simulated dataset, we calculated the standard deviation (SD) of ln(OR) and 95% CI of the estimated OR from bootstrap. We then calculated the ratio of SD and CI estimated from simple vs. clustered bootstraps using the same machine learning method. We grouped datasets into clustered or non-clustered datasets by ICC. Clustered datasets had ICC of 0.1, 0.25, and 0.4.

Figure 4 shows the ratios of SD and CI estimated from simple vs. clustered bootstraps using Lasso regression (panel A, C) and neural network (panel B, D) for clustered and non-clustered data. For non-clustered data, SD of ln(OR) and 95% CI estimated from simple and clustered bootstrap were similar (0% of datasets had ratios ≤0.9 or ≥1.1). But for datasets with a hierarchical clustering effect, simple bootstrap under or overestimated SD of ln(OR) and 95% CI in most cases compared to clustered bootstrap (85% of datasets had ratios ≤0.9 or ≥1.1).

This simulation study demonstrated that in the presence of clustered data in medical device research, using simple bootstrap without considering the clustered structure of data for standardization with machine learning methods can lead to under and overestimation of variance and CI of the device coefficient. Clustered bootstrap was feasible and more appropriate to take into account the provider clustering effect.

Standardization with machine learning methods has been shown to be a feasible method for comparative analyses. Medical device research could leverage this method to compare outcomes between device groups. Moreover, when conducting medical device research with hierarchical data, researchers should examine whether clustering exists and consider

using appropriate methods to obtain variance and confidence intervals for the device coefficient. Clustered bootstrap is preferred over simple bootstrap to obtain robust estimates of variance and confidence intervals for the device coefficient when performing standardization with machine learning methods.

Figure 4: Ratios of standard deviation (SD) of ln (OR) and 95% CI of OR

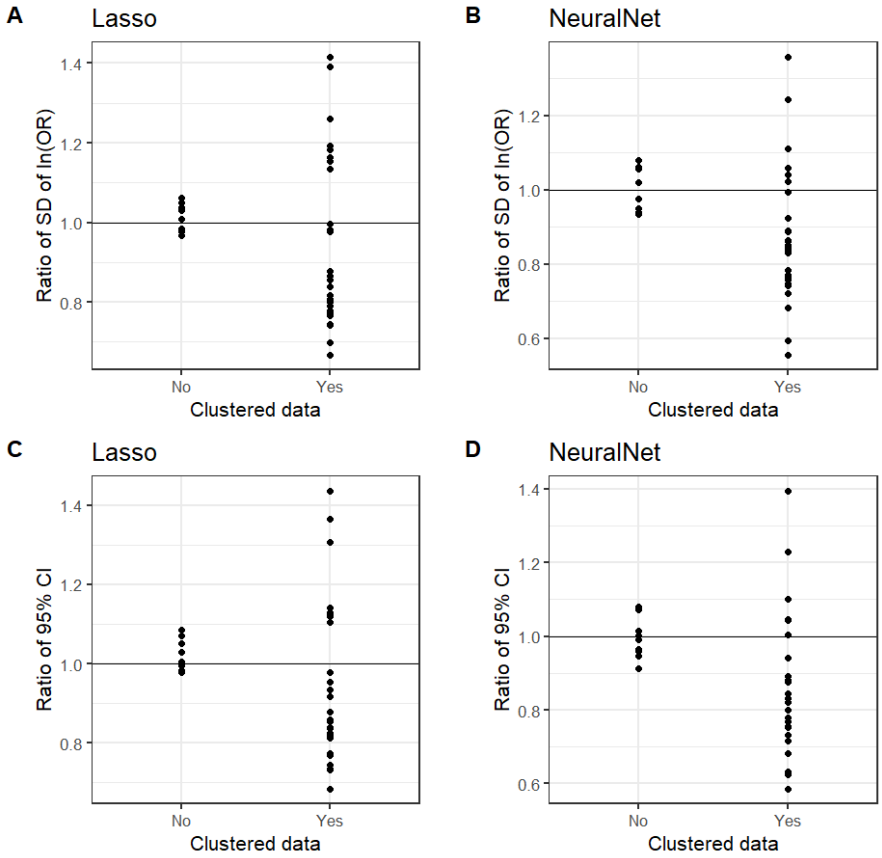


Figure 4. Ratios of standard deviation (SD) of ln(OR) and 95% CI of OR estimated from simple vs. clustered bootstrap for standardization with Lasso logistic regression and neural network models.

1.

OBJECTIVE 5

Developed a gender- and sex- specific outcome measure framework for devices and tested it in the most mature CRNs (e.g., in orthopedics, vascular, abdominal hernia).

In response to the growing body of evidence indicating that sex and gender may play significant roles in the course and outcome of condition and selected treatments,[134] the CDRH Health of Women Strategic Plan identified 3 priorities to encourage innovations in the research of, device development, and dissemination of sex- and gender-difference studies.[135] These priorities include (1) improving the availability, analysis, and communication of sex- and gender-specific information, (2) applying an integrated approach for current and emerging issues related to the health of women, and (3) developing a research roadmap for the health of women medical device ecosystem.

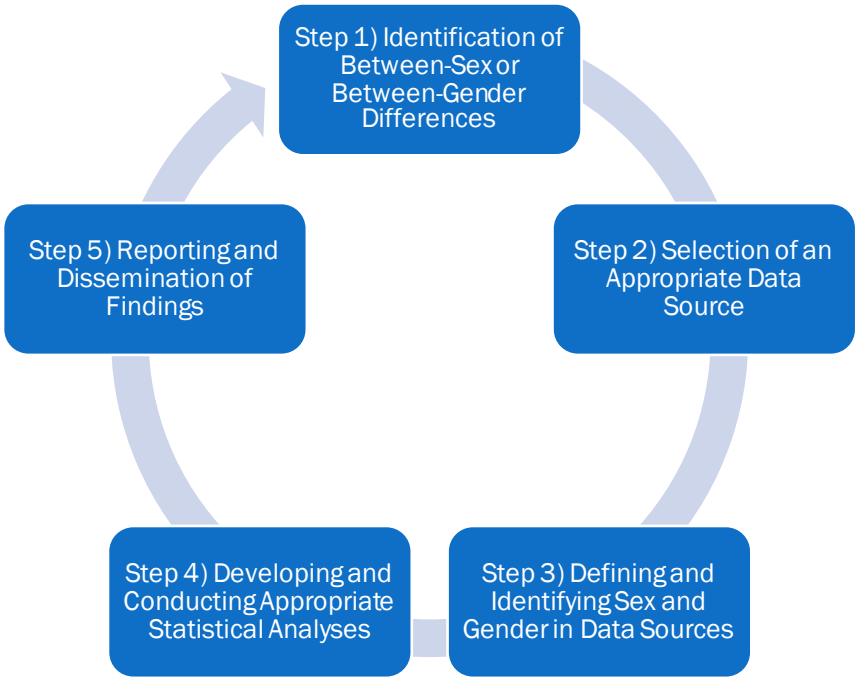
The following framework for sex- and gender- specific studies was developed based on the conducted studies within the CRNs, the lessons learned from these analyses, and the recommendations of the CDRH Strategic Plan,[136] Health of Women Strategic Plan[43] and CDRH Guidance on the Evaluation of Sex Specific Data on Medical Device Clinical Studies[42]. Figure 5: Framework for Sex and Gender Studies within MDEpiNet CRNs depicts the cyclical nature, where findings are used to improve CRN development and lead future research, are made possible through MDEpiNet's Collaborative Learning Communities.

[134] Food and Drug Administration: Center for Devices and Radiological Health. Evaluation of Sex-Specific Data in Medical Device Clinical Studies. Published online 2014:1-26. http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm283453.htm

[135] U.S. Food and Drug Administration Center for Devices and Radiological Health. The CDRH Health of Women Strategic Plan.

[136] U.S. Food and Drug Administration Center for Devices and Radiological Health. 2022-2025 Strategic Priorities. Published 2022. https://www.fda.gov/media/155888/download

Figure 5: Framework for Sex and Gender Studies within MDEpiNet CRNs



Identifying Between-Sex or Between-Gender Differences

Initial steps for conducting sex and gender studies within CRNs are to identify conditions, exposures, and outcome differences between sex and genders that can potentially be analyzed with CRN data. Several considerations are important to examine at this step. It is crucial to determine if there is biological plausibility for the suspected potential sex-difference, determine if sex-differences within the clinical areas of interest or within the devices of interest have been established, and compare any existing results between varying data sources. If a device is only used within one sex, then sex-difference studies do not need to be completed. Compiling prior research findings on these hypotheses can guide future hypotheses while preventing redundant research. If, through this process of review, gaps in knowledge or competing findings are found, it is indicative that a study should be done to determine why we see between sex or between gender differences and what steps can be taken to reduce inequalities in healthcare. Extracting this information is critical to informing the subsequent relevant protocol development.

Selection of Appropriate Data Sources

Any data utilized for the assessment of sex differences must be available, credible, relevant, and analyzable. Furthermore, it is crucial that the method used to collect the data, the original purpose of the data, and whether any validation of the data is performed are known and taken into consideration. Each data source can vary in quality.

Coordinated Registry Networks (CRNs) have been identified as a potentially powerful tools for post-approval studies evaluating the safety and effectiveness of medical devices.[137] The Coordinated Registry Networks (CRNs) bring together real-world data from a variety of sources, including multiple different registries, to further support the real-world evidence needed for comprehensive device evaluation.[138, 139] Registries that incorporate standardized data elements and standardized libraries for device identification, such as the Fast Healthcare Interoperability Resources (FHIR) and Systemized Nomenclature of Medicine – Clinical Terms (SNOMED) facilitate sex and gender identification. The standardization of data elements and device identifiers improve interoperability with other data sources and device identification capabilities. An additional type of data source that can be leveraged to conduct sex difference studies include claims. Claims produce procedure codes in the form of current procedural terminology (CPT) and International Classification of Diseases (ICD) codes that only identify whether a medical device-related procedure was performed. Given that these codes are input for billing purposes and not research purposes, they typically lack granularity in terms of which specific medical device was used. High-quality registries, however, can be linked to several claims databases such as the Center for Medicare and Medicaid Services (CMS) as demonstrated in the VISION-CRN and ORTHO-CRN. Claims complement registries by collecting patient-level characteristics, diagnoses,

[137] Food and Drug Administration: Center for Devices and Radiological Health. Strengthening Our National System for Medical Device Surveillance: Update and Next Steps. 2013;(April):11.
[138] Pappas G, Berlin J, Avila-Tang E, et al. Determining value of Coordinated Registry Networks (CRNs): a case of transcatheter valve therapies. *BMJ Surgery, Interv Heal Technol*. 2019;1:e000003. doi:10.1136/bmjsit-2019-000003
[139] Krucoff M, Normand S, Edwards F, et al. Recommendations for a national medical device evaluation system: strategically coordinated registry networks to bridge clinical care and research.

treatments, hospitalizations, and charges for inpatient as well as outpatient services.

Defining and Identifying Sex and Gender in Data Sources

The FDA's strategic priorities specify that observed differences associated with biological factors (sex) are of primary interest, however most medical device studies rely on patient self-reported values (gender).[27] It is therefore of paramount importance to define, identify, and differentiate between sex and gender in data sources. As previously mentioned, standardized definitions and elements, can be leveraged to accurately identify sex.

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The Office of the National Coordinator for Health Information Technology (ONC) United States Core Data for Interoperability (USCDI) version 3 data elements provide have guidance for defining and representing patient sex (at birth) and patient gender identity. More specifically, definitions for administrative gender, clinical sex, sex assigned at birth, legal sex, clinical gender, and gender identity are provided and summarized below.

Administrative Gender is defined as the gender that the patient is considered to have for administration and record keeping purposes. This property is often used as an input to patient matching algorithms, for example. Clinical Sex is a testable observation about a biological property of the patient. There are several different types of clinical sex, including karyotypic/genetic/chromosomal, gonadal, ductal, phenotypic, etc. Clinical sex observations are represented using observation, qualified with the appropriate clinical codes from LOINC and/or SNOMED. Sex assigned at Birth refers to the sex as documented on the birth registration. Some countries allow variations such as not yet determined, unknown, or undifferentiated, while others do not. Some countries also allow birth registration information to be updated. Legal Sex refers to the categorization of citizens by regional and national entities using a single legal sex value. The legal sex of a patient can vary from region to region and country to

country. A single patient may have multiple legal sex values at the same time in different jurisdictions. In case where the patient gender administrative property is not sufficient to communicate legal sex, realm specific extensions should be used. Clinical Gender refers to an observation about the patient, often collected as part of social history documentation, and represented as an observation. Clinical gender observations can provide both history and confidentiality, where the gender identity extension does not. Gender Identity is an indication from the patient about what gender they consider themselves to be. This can influence how the patient prefers to be addressed by care providers and other individuals. The standard gender identity extension may be used to communicate this property. This extension is appropriate when the gender identity is openly known.

Developing and Conducting Appropriate Statistical Analyses

The statistical analysis plan needs to consider the impact of sex in treatment selection and/or outcomes as well as potential factors that modify the relationship between sex and treatment selection and/or outcomes. Sex should not be simply treated as a predictive variable, there should be a systematic stepwise approach as below:

Stage 1 of the analysis focused on sex differences in patient selection for treatment and/or treatment outcomes. Investigators started by examining the characteristics of males and females and whether there is a difference in male and females' receipt of treatment and/or outcomes. Multivariable modeling was adopted in a staged approach, by fitting an additional set of covariates (demographics, socioeconomic variables, anatomical variables, comorbidities) at a time. The staged modeling approach may help understand possible reasons for sex differences in treatment selection and/or outcomes. In certain instances, it is important to have certain anatomic variable and ensure that the full assessment of its effect is considered.

Stage 2 of the analysis can focus on factors that may modify the relationship between sex and treatment selection and/or outcomes. Interaction between sex and a-priori defined important factors may be tested first to explore

potential effect modifiers. Stratified analyses can then be carried out to formally quantify the association between sex and treatment/outcomes within each subgroup.

Reporting and Dissemination of Findings

It is important to describe all methods employed in the sex-difference studies in detail. Transparency is important. Patient-, provider-, facility, and device-level characteristics are key elements to report. Study demographics in terms of proportion of the population included in each treatment arm and sex subgroup should be reported. Discussion regarding whether the proportions included in the study are consistent with the sex-specific prevalence of disease should be included. If outcome differences by sex are statistically significant and clinically meaningful, they should be reported in the results of the outcome analyses. If results of these analyses suggest a sex difference in an endpoint or event that is clinically meaningful but not statistically significant, they should be reported in the findings descriptively. Clinical plausibility is vital for the interpretation and reporting any results. Additionally, the limitations of the study, the evidence, and the device need to be discussed. Dissemination of the findings to patients, caregivers, clinicians, and the public shall be written in plain language. Communications should summarize how the study was conducted and sex-differences were evaluated, as well as the main findings, and the implications of the findings on clinical, patient, and regulatory decision-making.

Below are the example studies conducted using the CRN infrastructure:

ORTHO-CRN

Association of Sex with Risk of 2-Year Revision Among Patients Undergoing Total Hip Arthroplasty[140]

Total hip arthroplasty (THA) is a common and effective elective procedure for the treatment of end-stage osteoarthritis, especially among older

[140] Chen A, Paxton L, Zheng X, et al. Association of Sex With Risk of 2-Year Revision Among Patients Undergoing Total Hip Arthroplasty. *JAMA Netw open*. 2021;4(6):e2110687. doi:10.1001/jamanetworkopen.2021.10687

populations.[141] Although THA is associated with improved health-related quality of life,[142,143] some implants may fail and require revisions. With an aging population that includes more female individuals than male individuals, documented higher rates of THA among female individuals.[144,145] a greater prevalence of osteoarthritis,[146,147] and worse functional status among females,[148] it is important to examine the rate of THA revisions among female individuals compared to males. The main objective of the study by Chen et al. was thus to examine the differences in early revision surgery rates after primary THA between women and men. The secondary objective was to identify modifiers for the association between sex and all-cause revision.

The cohort study analyzed data obtained from the New York State Department of Health Statewide Planning and Research Cooperative System (SPARCS) and the California Office of Statewide Health Planning and Development (OSHPD). Chen et al. calculated the cumulative incidence of revision by sex using Kaplan-Meier analysis. Patients were censored at the time of revision or death or at the end of the study, whichever occurred first. The association of sex with the revision rate was then examined using a Cox proportional hazards regression model with a robust sandwich estimator to account for facility clusters. Three nested Cox proportional hazards regression models were run. The first model included sex as the sole explanatory variable. The second model adjusted for age, race/ethnicity, insurance status, and facility mean annual volume. In the third model,

[141] Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet (London, England)*. 2019;393(10182):1745-1759. doi:10.1016/S0140-6736(19)30417-9

[142] Gwam CU, Mistry JB, Mohamed NS, et al. Current Epidemiology of Revision Total Hip Arthroplasty in the United States: National Inpatient Sample 2009 to 2013. *J Arthroplasty*. 2017;32(7):2088-2092. doi:10.1016/j.arth.2017.02.046

[143] Konopka JF, Lee Y-Y, Su EP, McLawhorn AS. Quality-Adjusted Life Years After Hip and Knee Arthroplasty: Health-Related Quality of Life After 12,782 Joint Replacements. *JB JS open access*. 2018;3(3):e0007. doi:10.2106/JBJS.OA.18.00007

[144] Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am*. 2015;97(17):1386-1397. doi:10.2106/JBJS.N.01141

[145] Kurtz S, Mowat F, Ong K, Chan N, Lau E, Halpern M. Prevalence of primary and revision total hip and knee arthroplasty in the United States from 1990 through 2002. *J Bone Joint Surg Am*. 2005;87(7):1487-1497. doi:10.2106/JBJS.D.02441

[146] Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. *N Engl J Med*. 2000;342(14):1016-1022. doi:10.1056/NEJM200004063421405

[147] Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthr Cartil*. 2005;13(9):769-781. doi:10.1016/j.joca.2005.04.014

[148] Holtzman J, Saleh K, Kane R. Gender differences in functional status and pain in a Medicare population undergoing elective total hip arthroplasty. *Med Care*. 2002;40(6):461-470. doi:10.1097/00005650-200206000-00003

comorbidities were additionally adjusted. The analytical study cohort consisted of 65 109 patients in New York (49.0%) and 67 717 patients in California (51.0%) who underwent THA. The cohort included 74 002 (55.7%) women. The mean (SD) age of women was 67.1 (10.9) years, and the mean (SD) age of men was 64.2 (10.9) years. The all-cause revision rate was higher among women than among men according to the Kaplan-Meier analysis.

After adjusting for demographic characteristics and facility mean annual volume, the risk of revision was 20% higher among women compared with men (HR, 1.20; 95% CI, 1.11-1.31; $P < .001$). When comorbidities were added to the adjusted model, women had a 16% higher risk of revision (HR, 1.16; 95% CI, 1.07-1.26; $P < .001$). Revision rates differed significantly among women and men in the interaction analysis at both 1 and 2 years. In this cohort study, there was no clinically significant difference in the risk of all-cause revision between men and women at 2-year follow-up, even after adjusting for demographic, clinical, and facility-level characteristics. Although the differences in the general patient population were too small to conclude a significant association, we found a modest difference in the risk of revision in a small subgroup of women younger than 55 years compared with men in the same age group. Given the increasing number of younger people undergoing THA, future research should examine the factors associated with differences in the risk of revision by sex in a larger sample of younger patients with longer-term follow-up.

"*Early Revision after Primary Total Knee Arthroplasty*"- currently under review, Journal of Arthroplasty

Total knee arthroplasty (TKA) as a common procedure in knee osteoarthritis is project to grow substantially in the next decade with more than 12 million people living with a knee replacement. There is mixed evidence of sex as a risk factor for revision after TKA. The NY SPARCS and CA OSHPD administrative databases were used to study sex-difference in early all-cause, septic, and aseptic revision in primary TKA. The primary outcome of

interest was all-cause revision, defined as the addition, removal, or replacement of any implant component of the index TKA. Secondary outcomes were septic and aseptic revisions. Septic revision was defined by the presence of a concurrent diagnosis of infection at the time of revision. Revisions without a concurrent infection diagnosis were categorized as aseptic revisions. We used Kaplan Meier and Cox proportional hazard methods to estimate the association between sex and revision with various sub-groups: age, gender, insurance, race, and facility volume.

This study had total 212,385 patients who underwent TKA from 2015-2018 in California and New York State statewide databases. Our results show that mean age of the population was 67.2 years, where 62% were female. Total follow-up time was up to 3 years. The 2-year all-cause revision risk was 2.2% among males (95% confidence interval (CI) = 2.1% to-2.4%) and 1.7% among females (95% CI = 1.7% to-1.8%); and 2-year septic revision risk was 0.7% among males (95% CI = 0.7% -to 0.8%) and 0.4% among females (95% CI= 0.4% to -0.4%). In adjusted analysis, males had a 32% higher all-cause revision risk (HR=1.32, 95% CI = 1.22 to, 1.43, p-value < 0.001), and a 97% higher septic revision risk (HR=1.97, 95% CI =1.71 to, 2.26, p-value < 0.001) compared to the females. Further, males in all age groups had higher revision risk than females, and the effect was most prominent in patients <55 years. The results also show that aseptic revision risk was not significantly different in males and females. The study concluded that males had slightly higher revision than females. This is potentially attributed to difference between males and females found in septic revisions, where males had significantly higher risk of septic revisions. This suggests that younger males are the most at-risk population among the subgroups studied. This is an important information for clinicians to consider while consulting patients. Future research should focus on younger males to study this effect. Further, reducing infection risks in all patients is important in the success of TKA. This study is currently under review and the Journal for Bone and Joint Surgery.

ACH CRN

"Evaluation of treatment differences between males and females undergoing ventral hernia repair: An analysis of the Abdominal Core Health Quality Collaborative (ACHCQC)"[149]

Ventral hernia repair is one of the most common general surgery procedures, with more than 400,000 performed annually in the United States.[150] Sex disparities in regard to ventral hernia are not well understood and is emerging as an important clinical variable associated with surgical outcomes and clinical decision making. This study aimed to identify treatment differences between males and females undergoing ventral hernia repair using the Abdominal Core Health Quality Collaborative (ACHQC) database, a multi-institutional national hernia registry for quality improvement. The study cohort included adult patients undergoing elective umbilical, epigastric, or incisional hernia repair prior to May 2020. Treatments of interest for sex-specific differences included surgical approach (minimally invasive or open), mesh use, mesh type, mesh position, anesthesia type, myofascial release, fascial closure, and fixation use.

Two approaches were used to evaluate sex-specific differences in treatment choices while adjusting for clinical characteristics. The first approach utilized logistic regression where sex was analyzed as the outcome and treatment choices were included in the models as predictors with other baseline covariates and relevant prespecified interaction terms. Propensity score matching was used as the second approach. Each analysis was performed within each hernia type subgroup.

A total of 8489 umbilical, 1801 epigastric, and 16,626 incisional hernia repairs were identified from 308 surgeons at 283 sites. In the unadjusted analysis, females were less likely to undergo an open repair for both umbilical (70.6% vs 73.3%, p=0.017) and incisional (59.4% vs 63.3%, p<0.001). Mesh use was less frequent in females undergoing umbilical (59.4% vs 66.2%, p<0.001) and epigastric (71.5% vs 79.1%, p<0.001)

repairs, but not incisional hernia repairs (93.9% vs 94.3%, p=0.262). Mesh location differed amongst males and females for all three types of repairs. Mesh fixation was performed less frequently in females undergoing umbilical hernia repair (53.0 vs 60.6%, p<0.001) and permanent mesh was less likely to be used (97.2% vs 98.4%, p=0.007). Females had higher rates of myofascial release during umbilical hernia repairs (3.4% vs 1.9%, p<0.001), but lower rates during incisional hernia repairs (47.0% vs 49.5%, p=0.002). Logistic regression suggested operative approach was associated with sex for all three types of repairs (p<0.05), where MIS approach was found to be more commonly associated with females. The propensity scores matched analysis suggested females with incisional hernia were less likely to undergo an open repair (60.2% vs 63.4%, p<0.001) and have mesh used (93.8% vs 94.8%, p=0.02). In umbilical and incisional hernia repairs, females had higher rates of intraperitoneal mesh placement while males had higher rates of preperitoneal and retro-muscular mesh placement. This study has shown that small, but statistically significant, treatment differences exist between males and females. It remains unknown whether these treatment differences result in differing clinical outcomes and is a future direction of this study. The manuscript entitled "Evaluation of treatment differences between males and females undergoing ventral hernia repair:

VISION CRN

Association of Sex With Repair Type and Long-term Mortality in Adults With Abdominal Aortic Aneurysm[151]

We assessed the hypothesis that compared to men, women face a higher risk of death after AAA repair due to differences in disease severity and repair type using patients registered in the VQI-Medicare database between

[149] Polcz, Monica E et al. "Evaluation of Treatment Differences Between Men and Women Undergoing Ventral Hernia Repair: An Analysis of the Abdominal Core Health Quality Collaborative." Journal of the American College of Surgeons vol. 235,4 (2022): 603-611. doi:10.1097/XCS.0000000000000295

[150] Huerta S, Varshney A, Patel PM, Mayo HG, Livingston EH. Biological Mesh Implants for Abdominal Hernia Repair: US Food and Drug Administration Approval Process and Systematic Review of Its Efficacy. *JAMA Surg*. 2016;151(4):374-381. doi:10.1001/jamasurg.2015.5234

[151] Ramkumar N, Suckow BD, Arya S, et al. Association of Sex With Repair Type and Long-term Mortality in Adults With Abdominal Aortic Aneurysm. *JAMA Network Open*. 2020;3(2):e1921240-e1921240.

2003 and December 31, 2015. Our study cohort included patients aged 65 years or older who had an endovascular or surgical abdominal aortic aneurysm (AAA) repair recorded in the VQI and were linked to Medicare claims. The primary exposure was sex (women versus men), and the main outcomes were AAA repair type (surgical versus endovascular) and subsequent long-term mortality.

Among women, 27% received surgical versus only 18% of men. After balancing key risk factors, women were 1.7 times more likely to receive surgical versus endovascular procedures. The 10-year survival rate after AAA repair was 36% in men versus 28% in women. Subgroup analysis by repair type revealed that women experienced higher mortality rates after endovascular repair, while men and women faced a similar risk of death after open surgical procedures. After further stratification by symptom severity, higher risk of mortality in women was limited to elective open surgical and endovascular interventions for ruptured AAA.

Changes in the Long-term Risk of Adverse Outcomes in Patients Treated With Open vs Endovascular Abdominal Aortic Aneurysm Repair[152]

While the differences in short-term outcomes between males and females in abdominal aortic aneurysm (AAA) repair have been well studied, it remains unclear if these sex disparities extend to other long-term adverse outcomes after AAA repair, such as reintervention and late rupture. We performed a cohort study of 13,007 patients undergoing either endovascular (EVR) or open AAA repair between 2003-2015 using prospectively collected data in the Vascular Quality Initiative registries. Eligible patients were linked to fee-for-service Medicare claims to identify late outcomes of rupture and aneurysm-specific reintervention.

Although the 10-year rupture incidence was slightly higher for females, this difference was not statistically significant after risk adjustment. Likewise, we found no sex difference in reintervention rates, even after risk adjustment.

[152] Sedrakyan A, Goodney PP, Mao J, Beck AW, Schermerhorn ML. Changes in the Long-term Risk of Adverse Outcomes in Patients Treated With Open vs Endovascular Abdominal Aortic Aneurysm Repair. JAMA Surg. 2022 Aug 1;157(8):733-735. doi: 10.1001/jamasurg.2022.1070. PMID: 35648427; PMCID: PMC9161116.

Regression models suggest effect modification by surgery type for reintervention, where females who underwent index EVR had a higher risk of reintervention than males, while females who underwent OPEN were at a lower risk of reintervention compared to males; however, neither effect reached statistical significance. Additionally, we found that the risk of reintervention for females versus males varied across symptom status, where females were less likely to undergo reintervention after an elective or symptomatic repair but were more likely to undergo reintervention after a rupture repair. In sum, males and females undergoing AAA repair had similar rates of reintervention and aneurysm rupture in the 10 years following their procedure. However, our findings suggest that repair type and symptom status may affect the role of sex in clinical outcomes.

Carotid Stenosis Treatment and Outcomes

Manuscript under review

Stroke is a leading cause of death that disproportionately affects women. Treating carotid stenosis with carotid artery stenting (CAS) or carotid endarterectomy (CEA) can prevent ischemic stroke. Yet, the sex-specific use and long-term outcomes of these interventions remain unclear. We analyzed carotid revascularizations in the VQI-Medicare to identify long-term outcomes. Our study cohort included patients undergoing index CAS or CEA between 2005-2015 who were fee-for-service Medicare beneficiaries aged 65+. The primary exposure was sex, and the primary outcome was stroke. Using log-binomial regression, we estimated the relative risk for CAS treatment accounting for clustering by center. Cox proportional hazards regression was used to estimate the hazard ratio for stroke. We used inverse probability-weighted risk adjustment based on patient demographics, comorbidities, and disease severity for all analyses.

In our cohort of 22,341 eligible patients, women were less likely to undergo CAS than men. Women undergoing carotid revascularization had a 24% increased risk of stroke within 5 years of surgery following both CEA and CAS. This effect was most pronounced for symptomatic treatment, where women

undergoing CEA had a 3% higher risk-adjusted 5-year cumulative incidence of stroke. In sum, compared to men, women had a higher incidence of postoperative stroke after carotid revascularization.

Peripheral Vascular Intervention Outcomes

Manuscript under review

Endovascular peripheral vascular intervention (PVI) has become the primary revascularization technique used for peripheral artery disease (PAD), but there is limited understanding of long-term outcomes of PVI among women versus men. In this study, our objective was to investigate sex differences in the long-term outcomes of patients undergoing PVI. We performed a cohort study of patients undergoing PVI for PAD between January 1st, 2010 and September 30th, 2015 using data in the VQI registry. Patients were linked to fee-for-service Medicare claims to identify late outcomes including major amputation, reintervention, major adverse limb event (MALE), which included MALE, major amputation or reintervention, and mortality. Sex differences in outcomes were evaluated using cumulative incidence curves, Gray's test, and mixed effects Cox proportional hazards regression accounting for patient and lesion characteristics using inverse probability weighted estimates.

In this cohort of 15,437 patients, 44% (n=6,731) were women. Women were less likely to present with claudication than men or be able to ambulate. There were no major sex differences in lesion characteristics, except for an increased frequency of tibial artery treatment in men. Among patients with claudication, women had a higher risk-adjusted rate of major, but a lower risk of mortality. There were no sex differences in reintervention or MALE for patients with claudication. However, among patients with chronic limb-threatening ischemia, women had a lower risk-adjusted hazard of major amputation, MALE, and mortality. Therefore, there is significant heterogeneity in PVI outcomes among men and women, especially after stratifying by symptom severity. We found that women with claudication had a higher risk of major amputation, but an overall lower mortality rate. Men

with chronic limb-threatening ischemia had a higher risk of major amputation, MALE, and mortality.

During the course of the grant, the team actively looked for the opportunities to leverage CRN infrastructure to respond to critical national needs and gaps. Two examples related to pandemic response and novel IT technologies are depicted below.

PREPT

The Pandemic Response and Emergency Preparedness Task Force (PREPT) was convened by the Medical Device Epidemiology Network (MDEpiNet) and completed its White Paper on February 1, 2021. The Task Force brought together over 30 experts to produce 10 project areas that address the COVID-10 pandemic leveraging the CRN infrastructure. Gap analysis and concept proposals were created addressing complex issues faced by health care and medical product approval during the pandemic. Many of the proposals went on to be funded from public and private sources including Trial Design to Accommodate to a Rapidly Changing Pandemic: Blockchain and Artificial Intelligence: Tools to Improve Efficacy of RWE Collection, Aggregation, and Analysis: Systemic Harmonization and Interoperability Enhancement for Laboratory Data (SHIELD) and COVID-19. The collaborative space created by MDEpiNet demonstrated ability for rapid response to a national emergency.

BAIT

The Blockchain and Artificial Intelligence Taskforce (BAIT) was established to advance CRN collaborative learning community maturity by evaluating the potential impact of blockchain and artificial intelligence technologies on CRN's efficient collection of and sharing of data. To encompass relevant perspectives, stakeholders from industry, academia, and regulatory agencies, with both leaders and technical executers, were brought together to examine the impact of these technologies in 5 functional dimensions:

- Data collection and quality control
- Data harmonization and standardization
- Data aggregation and storage

- Data analytics
- Permissioning and consenting frameworks

The white paper prepared by BAIT proposes two use-cases to test the implementation of blockchain technologies and three use-cases to test artificial intelligence methodologies within the framework of collection and use of medical device data for research and regulatory decision-making.[153] Additionally, two manuscripts adapted from BAIT's findings are in progress to publicly disseminate BAIT's findings. [154,155]

CRN Architecture

The CRN Architecture work aims to bring together the collective resources, tools, and roadmap for the CRN Collaborative Learning Community to address the following shared challenges:

- Defining processes to identify, specify, and formalize clinical concepts as common data elements.
- Implementing the use of common data elements to capture standardized data that supports the use, analysis, and exchange of data across therapies, patient populations and episodes of care
- Incorporating the Unique Device Identification (UDI) as an index to empower CRNs to become fit for purpose to routinely study device-specific questions.
- Advancing patient-reported data to enable the research community to link patient experiences to clinical data sources and facilitate the regulatory assessment of device performance, including patient-centric endpoints applicable to future studies.
- Establishing a framework to build a sustainable partnership business infrastructure to allow for national or international

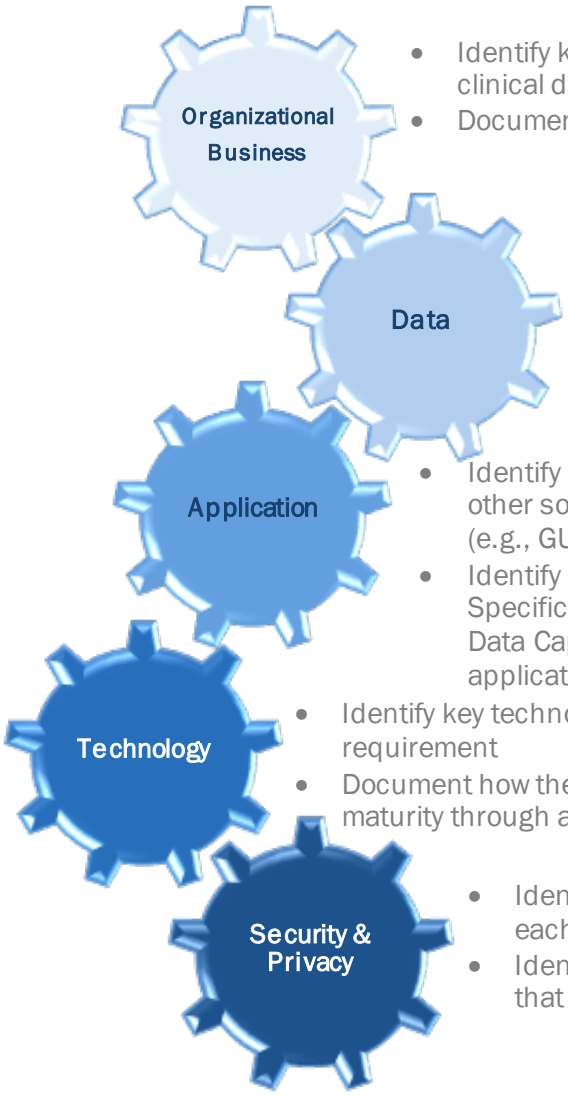
[153] Alterovitz, G., Simonyan, V., Yesha, Y., Baulier, J., Crafts, M., Curbera, F., D'Haese, P.-F., Drozda Jr, J., Duvall, S., Ege, G., George, E., Henry, W., Honavar, V., Iorga, M., Kaminski, C., Kuntz, R., Lilley, P., Linton, J., Mylrea, M., ... Kaminski, E. Blockchain and Artificial Intelligence Taskforce (BAIT) White Paper. In Progress.

[154] Koonce, R. M., Gressler, L. E., Honavar, V., Simonyan, V., Yesha, Y., Rosè, C. P., Altorovitz, G., & Marina-Dabic, D. (n.d.). Promises of Artificial Intelligence in the Strategically Coordinated Registry Networks (CRNs): Recommendations from the BAIT Part 2. *In Progress*.

[155] Koonce, R. M., Gressler, L. E., Simonyan, V., Yesha, Y., & Marinac-Dabic, D. (n.d.). The Integration of Blockchain Technology within the MDEpiNet Coordinated Registry Networks: Report by the Blockchain and Artificial Intelligence Taskforce (BAIT) Part 1. *In Progress*.

coverage over an extended period that can be applied more broadly across the medical device landscape.

- Ensuring that patient privacy, protecting personally identifiable information (PII) and data security is established and maintained by the CRNs, as well as complying with requirements for protected health information (PHI).



- Identify key organizational or business-related issues (specific to the clinical domain) that need to be addressed.
- Document the common and clinical domain-specific requirements.

- Develop a process to establish a minimum core data set – i.e., taking the vetted clinical concepts and building out logical models and informatics mappings to vocabulary and exchange standards
- Investigate options for maintaining and governing the common data elements in a publicly accessible platform

- Identify and document any public APIs – e.g., SMART on FHIR® apps or other solution interfaces that would be available for use by the CRNs (e.g., GUDID APIs)
- Identify and aid in the alignment with key Exchange Standards – Specifications and Implementation Guides (e.g., US Core, Structured Data Capture, etc.) being implemented and/or found in reference applications, which may be leveraged by CRNs

- Identify key technologies that will address specific CRN needs by type of requirement
- Document how the CRNs can leverage technologies to advance the CRN's maturity through an improved architecture

- Identify unique privacy requirements that need to be addressed by each of the CRNs (e.g., PII, PHI, etc.)
- Identify strategies (e.g., technologies) that are leveraged by CRNs that may be emulated by less mature CRNs

Sedrakyan A, Marinac-Dabic D, Campbell B, Aryal S, Baird CE, Goodney P, Cronenwett JL, Beck AW, Paxton EW, Hu J, Brindis R, Baskin K, Cowley T, Levy J, Liebeskind DS, Poulose BK, Rardin CR, Resnic FS, Tcheng J, Fisher B, Viviano C, Devlin V, Sheldon M, Eldrup-Jorgensen J, Berlin JA, Drozda J, Matheny ME, Dhruva SS, Feeney T, Mitchell K, Pappas G. Advancing the Real-World Evidence for Medical Devices through Coordinated Registry Networks. BMJ Surg Interv Health Technol. 2022 Nov 11;4(Suppl 1):e000123. doi: 10.1136/bmjsit-2021-000123. PMID: 36393894; PMCID: PMC9660584.

U.S. Food and Drug Administration CDRH. Strengthening Our National System for Medical Device Postmarket Surveillance: Update and Next Steps. U.S. Food and Drug Administration (FDA). https://www.fda.gov/media/84409/download. Published 2013. Accessed 07 August2019

U.S. Food and Drug Administration (FDA) CDRH. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Guidance for Industry and Food and Drug Administration Staff U.S. Food and Drug Administration (FDA). https://www.fda.gov/media/99447/download. Published 2017. Accessed 07 August2019

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1. **Promotion of unique device identification (UDI):** The precise identification of medical devices is essential for evaluating the performance over time. Currently, most registries use manufacturer names, device names or billing codes for product identification, but this is mostly inadequate for unique product identification. Both regulators and MDEpiNet now advocate use of Unique Device Identification (UDI) system.[a] The FDA UDI rules require manufacturers to assign unique identifiers to their marketed devices and submit required device attributes to a UDI Database. In the U.S., the FDA's Access GUDID, a public portal of the Global Unique Device Identification Database (GUDID), serves this purpose.[b] By providing a unique numeric or alphanumeric code for each device model and an identifier that includes the production information for that specific device (e.g., serial number, manufacturing date), the UDI delivers the most accurate way to identify and track medical devices.

Device Identification domain describes the registry's ability to uniquely identify a device. Ideally, the UDI would be included; however, when unavailable, the registry should capture a combination of identifiers that enables unique identification of the device (e.g., catalog number, manufacturer, brand or generic name, device description).	Level 1 *Early Learner*	The registry or a linkable database in a CRN is capturing device information that is available under CPT, ICD, or other generic coding for the device-based procedure. [i]
	Level 2 *Making Progress*	The registry or a linkable database in a CRN is capturing device information using at least manufacturer and specific device names and leverages relevant CPT, ICD, or other generic coding system. [i]
	Level 3 *Defined Path to Success*	Building from level 2 achievements, the CRN has conducted large scale demonstration project to include manufacturer's product catalog numbers or UDI that included at least five percent of annual patient enrollment.
	Level 4 *Well Managed*	The registry or a linkable database in a CRN is routinely capturing device information with manufacturer's product catalogue numbers or UDI that can identify devices and mapped to attributes/features needed for research and surveillance.
	Level 5 *Optimized*	The registry or a linkable database in a CRN is routinely capturing device information with UDI and mapping to attributes/features needed for research and surveillance. UDI information is seamlessly and efficiently integrated with the registry or CRN operations.

2. **Improving data collection efficiency:** Minimizing the burden of data collection processes is crucial, to maximize data submission. Centers with advanced informatics are able to organize their clinical workflows to record data needed for registries in ways that reduce effort and so improve the completeness of data collection.[c] This kind of structured data capture minimizes the number of staff needed for data collection and the time they need to spend. Agreements about the core vocabulary and corresponding technical (database) representation allow integration of high-quality data into the processes of care; promotion of automated collection; lowering the burden of data collection; minimization of human error; and reduction of resource requirements. Efforts to reduce the burden of data collection and improve the quality of data include scanned capture of UDI on device labels and auto-population of key device attributes from Access GUDID. Access GUDID offers means to auto-populate fields such as manufacturer, brand, device size, and other standard fields needed for analysis. Finally, soliciting patient input and collecting data through innovative patient-facing applications enables inclusion of endpoints of interest, addressing patient preferences and gaining further efficiencies in data collection.

Efficiency domain describes the extent to which the registry is embedded in the healthcare quality improvement system so that data collection occurs as part of care delivery (i.e., not overly burdensome, not highly complicated, not overly costly) and integrated with workflow of clinical teams. A key pre-condition for this domain is that the core minimum data process with key stakeholders is developed in order to define the CRF and the elements are clinically relevant and harmonized. This will ensure that reliable and relevant data elements with proper definitions are included in the data collection effort.	Level 1 *Early Learner*	Heavy burden of data collection with ad hoc data elements on a project basis but without agreement on clinically relevant core minimum data elements.
	Level 2 *Making Progress*	Clinically relevant core minimum data elements are established with key stakeholder input. Data collection is started but there is a heavy burden on data collectors (manual data entry with no automation).
	Level 3 *Defined Path to Success*	In addition to level 2 achievements, technologies are in place (e.g., structured data extraction from EHRs; mobile apps) to reduce burden on data collectors, and a pilot project is completed on adoption of data and terminology standards that will enable exchanges between data information ecosystems (interoperability).
	Level 4 *Well Managed*	Technologies are in place (e.g., structured data extraction from EHRs; mobile apps) to reduce burden on data collectors, and a multisite demonstration project is completed on adoption of data and terminology standards that will enable exchanges between data information ecosystems (interoperability).
	Level 5 *Optimized*	Technologies are in place (e.g., structured data extraction from EHRs; mobile apps) for all core minimum data elements and a fully automated data collection for most core minimum data elements, and there is a full adoption and integration of data and terminology standard (assumes complete interoperability).

3. **Advancing data quality for regulatory decision-making:** A key tenet of the CRNs construct is the development and adoption of discipline-specific core minimum data in collaboration with regulators. This includes reaching agreement on precise definitions of data elements. Consecutive data collection and completeness (minimizing missing or out-of-range values) are important in producing robust medical device evidence and CRNs strive to achieve adequate enrollment with complete records of the target population. Coverage (i.e., regional, national, health system etc.) is another important quality measure; and adequate coverage of hospitals and community practices within the scope of the registry is important for evidence generalizability.

Data Quality domain focuses on relevance, coverage (scale), completeness of patient enrollment and data elements (records) at both baseline and follow-up, and accuracy verified by periodic audits (ideally annually or at least every two years). These four concepts account for the relevance and reliability concepts outlined in the real-world evidence guidance issued by the Center for Devices and Radiological Health at the FDA. A key pre-condition for this domain is that the registry core minimum data elements and research modules are defined in collaboration with key stakeholders. This will ensure relevance because data elements with proper definitions and key stakeholder input are included in the data collection efforts (see also TPLC domain). Coverage (scale) concept is related to extent of participation of sites that use particular a technology/device. Completeness concept is related to how complete	Level 1 *Early Learner*	The coverage includes the pilot registry/ CRN with single or several site efforts that capture small patient populations (data completeness and other quality measures are not yet relevant).
	Level 2 *Making Progress*	The coverage includes a large number of sites (large population) but mostly inadequate enrollment [ii] of patients but robust completeness [iii] of data elements (records). Plans are in place for conducting audits to assess and improve the data quality.
	Level 3 *Defined Path to Success*	The coverage includes a large number of sites engaged (large population), there is adequate enrollment [ii] of patients and completeness [iii] of data elements (records). Plans for conducting and executing audits of data quality at least once with minimum* requirements.
	Level 4 *Well Managed*	The coverage is at least regional or includes a large national health system with adequate enrollment [ii] of patients and completeness [iii] of data elements (records). Ongoing sequential audits with at least one audit completed with moderate* requirements.
	Level 5 *Optimized*	The coverage is national with adequate enrollment [ii] of patients and completeness [iii] of data elements (records). Initiating routine audits with extensive* requirements (at least bi-annual).

the enrollment is at each site and the core minimum data (records). Accuracy is defined by the degree of matching of the CRN/registry data to the source documents. **Auditing requirements: Minimum includes verification of at least exposure (e.g., device) and outcomes using a generalizable cohort; moderate includes verification of exposure (e.g., device), outcomes and key risk factors using a generalizable cohort; and extensive includes verification of entire data collection forms using a generalizable cohort.*		
4. **Considering Total Product Life Cycle (TPLC) research:** Generating evidence from the time of early adoption of technologies is an important priority to support attainment of startup funds. Registries for breakthrough technologies can be designed to include specific factors needed for evaluation of effectiveness (e.g., Transcatheter aortic valve replacement (TAVR)); and to facilitate later transformation into a quality registry, by ensuring collection of minimum core data fields necessary for surveillance. A key issue is to not confuse the purpose of the registry with specific investigations that should be 'nested' within it: the latter can include collection of additional data elements. Using RWE in clinical trials is feasible, particularly in 'pragmatic trials' where patients and device operators included are broadly representative of the target population. To evaluate long-term outcomes, mature CRNs need to demonstrate robust linkage with relevant data sources that enable enhancement of data and longitudinal follow-up. [d] [e]		
TPLC domain describes the total life cycle of a device and the notion that registries can serve as the infrastructure for conducting both clinical research and device surveillance at different stages of device evaluation. Registry core minimum data elements and research modules	Level 1 *Early Learner*	Developed a plan for conducting short-term or long-term clinical outcome studies (e.g., direct follow-up or data linkages) and surveillance.
	Level 2 *Making Progress*	Developed some capacity (e.g., IT infrastructure system) for conducting short-term or long-term clinical outcome studies and surveillance.
	Level 3 *Defined Path to Success*	Registry has experience with at least one short-term or long-term clinical study or surveillance during product lifecycle that assists regulatory decision making. However, it has limited capacity for analytics and burdensome/ inadequate [iv] process to obtain long-term outcome data (e.g.,

should ensure relevance of the collected data from stakeholder perspective (see also Data Quality domain). In addition, the use of registries may allow for a seamless integration of evidence generation at the point of care throughout the device life cycle. A critical aspect of lifecycle research is obtaining long-term outcome data with efficient methodology. This domain is aligned with FDA's TPLC vision.		linking registry to EHRs or claims data) for research and surveillance.
	Level 4 *Well Managed*	Registry has experience with at least one study during the product lifecycle that assists regulatory decision making. Developed sustainable capacity for analytics and an adequate [iv] process to obtain long-term outcome data (e.g., linking registry to EHRs or claims data) for research and surveillance.
	Level 5 *Optimized*	Registry has substantial experience (e.g., three or more studies) that assisted regulatory decision making, has sustainable capacity for analytics, and an adequate [iv] process to obtain long-term outcome data (e.g., linking registry to EHRs or claims data) for research and surveillance.
5. **Establishing governance and ensuring sustainability:** MDEpiNet emphasizes strong governance and sustainability as essential issues for the CRNs. Even if a CRN is mature in many domains, any registry that is solely funded as a pilot study or by a standalone manufacturer will cease to exist once the organization has achieved its short-term goals. Sustainability requires multiple stakeholders to buy into the value that is generated by the CRN. CRNs that are hosted by a professional society or health system, with multiple funding sources and transparent leadership and governance, are most likely to be sustainable in the long-term. MDEpiNet promotes creating a 'Steering Committee' as well as 'Research and Publication' and 'Sustainability' subcommittees to engage stakeholders and to create multiple leadership opportunities for dedicated and enthusiastic experts. Holding annual think-tanks or meetings with stakeholders helps to achieve alignment and priority setting for infrastructure and research. Creating an atmosphere of collaboration and developing trust will enrich a CRN and is key to establish and sustain the continuous dialogue in supporting a learning (healthcare) system of medical device evaluation.		
<u>Governance and Sustainability</u> domain describes the governance structure focusing on participation of major stakeholders enabling generalizable (regionally, nationally or health system wide) data collection and transparent	Level 1 *Early Learner*	Absence of professional society/major health system/state endorsement, mostly pilot and project level governance.
	Level 2 *Making Progress*	Absence of professional society/major health system/state endorsement. Reasonable funding is available (e.g., support for a specific project at NIH R01 level or industry sponsorship at the same level).
	Level 3	

governance*. The hosting organizations include professional societies, integrated health systems, payers, and various states. In addition, the ability for the registry to obtain major and diverse sources of funding is critical for sustainability. Registries and CRNs built by manufacturers for their own purposes are special instances that are not in scope of this domain. **Transparent governance metrics include but are not limited to participation of major stakeholders and clear organizational structure with steering committee, subcommittees, and data access policies.*	*Defined Path to Success*	Hosted by a professional society/major health system/state. Reasonable funding is available (e.g., support for a specific project at NIH R01 level or industry sponsorship at the same level), establishing transparency in governance.
	Level 4 *Well Managed*	Hosted by a professional society/major health system/state. Robust funding is available (e.g., multi-year large scope projects funding in place at NIH center grant level or multiple industry sponsorship at the same level), and governance is transparent.
	Level 5 *Optimized*	Hosted by a major professional society/major health system, commitment to funding indefinitely (e.g., renewable NIH center grant level or multiple industry sponsorship at the same level), and governance is transparent.
6. Leveraging registries as quality systems: Most healthcare enterprises participate in registries as tools for quality improvement. Analyses of processes and outcomes from registries serve as feedback to inform the sites about conformance with guidelines, comparative patient outcomes, opportunities to improve care, and other critical strategic, administrative, and operational imperatives. Device use and outcomes are considered part of this function. [f] This infrastructure will enable medical device research and surveillance in the context of both the device and the device operator's performance. Lessons learned from cardiology, cardiac surgery and vascular surgery registries can be very helpful for the evaluation and improvement of care. [g] [h] [i] [j] Sharing best practices in provider feedback, such as use of creative data visualization techniques, can enhance clinician and hospital participation in quality improvement registries.		
<u>Healthcare Quality Improvement</u> domain describes the registry process for quality improvement. The registry is a healthcare delivery improvement system or is evolving into	Level 1 *Early Learner*	Registry does not have provider feedback benchmarking process and conducts limited device outlier assessments.
	Level 2 *Making Progress*	Registry has more than one, and growing number of participants in provider feedback benchmarking process and conducts limited device outlier assessments.
	Level 3	

one as device technologies are diffused into practice and need continuing evaluation (including outlier identification). The registry has established mechanisms to bring about beneficial change in healthcare delivery through stakeholder participation, ownership, and integration into the relevant healthcare systems.	*Defined Path to Success*	Registry has initiated routine provider feedback for all participating sites. As part of that process, it is developing routine device outlier assessment.
	Level 4 *Well Managed*	Registry has completed first major periodic feedback process. As part of the process, it has initiated device outlier assessment.
	Level 5 *Optimized*	Registry has regular and ongoing (at least annually or similar) provider feedback in place and routinely includes device outlier assessment. Ideally, there is automation of quality process with advanced analytics and visualization tools integrated with data collection.
7. **Incorporation of *p*atient generated data and PROs:** Patient generated data and PRO collection is an important priority of the FDA and other regulators, for safety and efficacy in medical devices. [k] Patients can contribute is by serving as partners, participating in research and surveillance, and sharing their experience related to devices. Robust and comprehensive patient generated, and PRO data collection is possible when combined with use of mobile applications, advancement in EHR systems and linkages to EHRs and registries. [l]		
The PRO measures should include collecting at least one general health and one disease-specific outcome measure. Center for Devices and Radiological Health at the FDA defines the PRO as a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.	*Level 1* *Early Learner*	The CRN identified (ideally with patient engagement) and collaborated with stakeholders to define disease specific and general health validated PROs that meet regulatory guidelines.
	Level 2 *Making Progress*	In addition to level 1, the CRN conducted a demonstration project of obtaining PROs and integrating within CRN infrastructure.
	Level 3 *Defined Path to Success*	In addition to level 2, the CRN is able to seamlessly integrate PROs within CRN infrastructure using patient-facing applications.
	Level 4 *Well Managed*	In addition to level 3, the CRN is routinely obtaining PROs using a consecutive and generalizable sample and using these for research and surveillance and has conducted at least one study using PROs for a benefits and harms assessment of technologies.
	Level 5 *Optimized*	In addition to level 4, the CRN is routinely obtaining PROs on a large scale to allow benchmarking at the participating institutional level and has substantial experience of using PROs for a benefits and harms assessment of technologies.

Notes for Appendix:

[i] Level 1 and level 2 achievements can be sufficient if only one device and few devices are on the market and if such coding would appropriately identify the device. In all other instances, catalog numbers and ideally UDIs are required.
[ii] Greater than 80% regional, national, or major health system coverage might be adequate.
[iii] Greater than 80% enrollment with complete records might be adequate.
[iv] If direct follow up is conducted, greater than 80% achievement might be adequate. When using data linkages, greater than 90% might be adequate.

References for Appendix:

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Note: This file can be viewed without login to the file share.

CRN Specific Minimum Core Data Elements

The following tables include the minimum core data elements for the respective CRN. These data elements are in various stages of development at the time of this publication. Details of these efforts are provided in Section 1C – CRN Minimum Core Data Elements.

The available CRN Minimum Core Data Elements are presented in alphabetical order below:

Women's Health Technologies

The following table includes the minimum core data elements that are identified:

Table 5: WHT Minimum core data elements

Clinical Workflow	Data Element
Patient Information	Patient identifier
	Ethnicity OMB.1997
	Gender [HL7v3.0]
	Race OMB.1997
	Preferred Language ISO 639.2
	[#] Pregnancies
	Pregnancy status
	History of major abdominal surgery
Evaluation	Adenomyosis
	Bladder problem (finding)
	Irregularity of menstrual cycle
	Complaining of pelvic pain (finding)
	Pain during sexual activity
	Dysphoria - depression
	Endometriosis of uterus
Management	Date of Procedure
	Procedures Performed
	Concomitant Procedures Performed
	Unique Device Identifier
Outcomes	Post Operative Complications
	Device involved in patient safety event or unsafe condition [AHRQ]

CATNIP

The following table includes the minimum core data elements that are identified:

Table 6: CATNIP Minimum core data elements

Clinical Workflow	Data Element
Patient Information	Patient identifier
	Ethnicity
	Gender
	Race
Evaluation	Obesity History
	Weight Loss History
	Functional Health Status
	Diagnosis of Type 2 DM or prediabetes (if yes, answer next 4 Qs)
	Hyperinsulinemia without hyperglycemia
	Diabetes diagnosed, controlled by diet and exercise
	Diabetes Mellitus Requiring Therapy with Non-Insulin Agents
	Diagnosis of obstructive sleep apnea (if yes, answer following Qs)
	Moderate to severe sleep apnea requiring oral appliances CPAP/BiPAP (or similar technology)
	Severe sleep apnea with significant hypoxia or complications (pulmonary HTN); using O2
	Diagnosis of Gastroesophageal Reflex Disease (GERD) (if yes, answer next Qs)
	Intermittent or variable symptoms, not requiring a response (evaluation/medication)
	Regular medication use (H-2 blockers/ low-dose PPI)
	Meet criteria for anti-reflux surgery
	Symptom: Pain with ambulation requiring nonnarcotic analgesia
	Symptom: Pain with ambulation requiring narcotic analgesia
	Hyperlipidemia controlled with Medication
	Hyperlipidemia poorly controlled with medication
	Diagnosis of Hypertension (If yes, then answer Qs below)
	Controlled by diet and exercise
	Hypertension Requiring Single Medication
	HTN requiring treatment with multiple medications
	Mood Disorder/Depression
	Hb A1C
	Fasting Glucose
	Triglyceride

	Total Cholesterol
	EGD/Endoscopy
	Upper GI/Esophagram
	Gastroesophageal Endoscopic Assessment/ EGD
	Esophagitis-Eosinophilic
	Peptic Ulcerations
	Duodenal Ulcerations
	Large Hiatal Hernia
	Patulous pyloric channel
	H Pylori (breath test, blood test)
	Phentermine
	Topiramate
	Saxenda
	Medications assoc. with weight gain
	SSRIs with weight gain
	Beta-blockers
	Proton pump inhibitors
	Anti-hypertensives
Management	Type of anesthesia
	General
	Local/Sedation
	None
	Type of Center where device implanted
	None
	Surgery Center
	Hospital
	Office
	Concomitant procedure required for placement (CPT code)
	Endoscopy
	Laparoscopic procedure
	Angiography
	Other
	None
	Duration of implantation procedure (duration of effect)
	Procedure aborted / incomplete
	Procedure reversibility /permanent anatomic change
	Revision/Correction (non-primary)
	Type of Concurrent obesity therapy:
	Medication
	Diet Counseling
	Exercise Counseling
	Intensive Behavioral /Lifestyle Therapy
	If Behavioral therapy/support group, moderate or intensive
	Minimal

	Moderate
	Intensive
	Patient Compliance
	Daily caloric reduction
	Exercise
	Type of Concurrent obesity therapy:
	Medication
	Diet Counseling
	Exercise Counseling
	Intensive Behavioral /Lifestyle Therapy
	If Behavioral therapy/support group, moderate or intensive
	Minimal
	Moderate
	Intensive
	Patient Compliance
	Daily caloric reduction
	Exercise
	Device Type- mode of action
	Space occupying
	Nerve stimulation
	Malabsorption/bypass
	Ablation
	Delayed emptying
	Procedure Access site
	Endoscopic
	Swallow/ PO
	Transabdominal/Laparoscopic
	Open Surgical
	Percutaneous
	Intravascular
	Device location
	Artery
	Intra-gastric/intra luminal
	Mouth
	Intraperitoneal/abdominal cavity
	Expected indwell time of device
	Expected durability of treatment effect
	Use outside of indications for Use/Off-label Use
	Expected Retrieval Procedure (types of retrieval)
	Endoscopic
	Spontaneous expulsion
	Surgical intervention
	None
	Index case retrieval procedure/ Procedure employed in this index case
	Primary Device

	Space Occupying Device (*Length and Diameter)
	Intravascular Catheter/Beads (*Length and Diameter)
	Intralumenal Stent Device (*Length and Diameter)
	Diversion Devices
	Band Device
	Details may include:
	Unique Device Identifier (includes the Primary UDI-DI Number and Production Identifiers)
	Company Name
	Brand Name
	Version or Model
	Catalog Number
	GMDN Preferred Term Code (if available)
	GMDN Preferred Term Name
	GMDN Preferred Term Definition
	Device Description
	Clinically Relevant Size
	*Size Type (Length, Area, Weight, Total Volume, Gauge, Angle, Pressure, Diameter (outer/inner))
	Size Value
	Size Unit of Measure
	Size Type Text (if length or diameter is provided as unstructured value)
Outcomes	**Perioperative / Periprocedural**
	Extended Hospitalization > X days past expected post-procedure recovery
	Treatment for dehydration as an outpatient
	Was the patient seen in an emergency department (ED) without admission?
	Interventions/ Reoperations (i.e., 30 Day Postoperative Occurrences)
	Unplanned reoperation within the 30 day postoperative period
	Other Surgical Occurrences (revision due to complication?)
	Metabolic/Bariatric Postoperative Occurrences (Bridging procedure?)
	Planned intervention (risks/interventions inherent in use and placement of device)
	Intervention type (revision, removal, etc.)
	Cause/reason for intervention
	Follow-Up / Post-Operative Visits
	Frequency of scheduled Follow-Up
	Scheduled device manipulations/adjustments
	Frequency of device evaluations/adjustments
	Adverse Events

	Was this a Serious Adverse Event
	Life-threatening AE?
	AE resulting in Device Removal or replacement
	Unscheduled outpatient Visit
	Device Intolerance
	Device-related Adverse events
	Procedure-related Adverse event
	Corrective action to treat AE:
	Reoperation
	Outpatient visit
	Hospitalization
	Infusion therapy
	Device Migration
	Device Failure/malfunction (indicate type)
	Deflation
	Fracture
	Other
	Did Device Failure/Malfunction require removal
	Did Failure/Event require Corrective Therapy
	How was Device failure event treated
	Surgical
	Endoscopic Therapy
	Medication
	Hospitalization
	Specific Adverse Events to be Followed and Reported
	Gastrointestinal ulceration
	Small bowel obstruction
	Gastric Perforation
	Nausea and vomiting causing dehydration
	Dysphagia
	GERD
	Abdominal Pain (if so, then did it require narcotic analgesia)
	Pulmonary Aspiration
	Weight Regain

Devices used for Acute Ischemic Stroke Intervention (DAISI)

The following table includes the minimum core data elements that are identified:

Table 7: DAISI Minimum core data elements

Clinical Workflow	Data Element

Patient Information	Age at Procedure Characteristics
	Gender
	Race
	Primary Insurer
	Height (inches)
	Height (cm)
	Weight (lbs)
	Age at Procedure Characteristics
Evaluation	Chronic obstructive pulmonary disease
	Diabetes
	Dialysis
	Hypertension
	Atrial Fibrillation
	Hyperlipidemia
	Prior Congestive Heart Failure
	All Head and Neck Computerized Tomography /Computed Tomography Angiography/Computed Tomography Perfusion
	All head and Neck Magnetic Resonance- Magnetic Resonance Imaging/ Angiography/ Perfusion-weighted MRI
Management	Admit Date
	Visit Code
	Transferred From?
	CAD Symptoms
	Prior Stroke Event
	Pre-op Hemoglobin (g/dl)
	Pre-op Hemoglobin (g/L)
	Creatinine (mg/dl)
	Creatinine (umol/L)
	Blood Pressure On Arrival - Systolic
	Diastolic
	International Normalized Ratio
	Glucose
	Pre-Op American Society of Anesthesiologists Physical Status Classification
	Pre-Op P2Y12 Antagonist
	Pre-Op Statin
	Pre-Op Chronic Anticoagulant
	IV Tissue Plasminogen Activator (tPA) Given
	Procedure Characteristics Date
	Primary Physician
Evaluation (continued)	Assistant
	Medicare Health Insurance Claim Number
	Hypercoagulable State

	Ipsilateral
	Contralateral
	Initial Location of Occlusion
	Side of Occlusion
	Location of Additional Occlusion
	Side of Additional Occlusion
	Expanded Thrombolysis In Cerebral Infarction Grade
	Trial Enrollment
	American Society of Anesthesiologists Class
	Anesthesia
	Intubated Prior to Angio Suite Arrival
	Time at Arrival to Angio Suite
	Time at Groin Puncture
	Stroke Onset to Groin Puncture
	ED Arrival to Groin Puncture
	Number of Passes
	Pass 1 Intervention Type
	Pass 2 Intervention Type
	Final Pass Intervention Type
	Pass 1 Clot Location
	Pass 2 Clot Location
	Final Pass Clot Location
	Pass 1 Guide Cath Balloon
	Pass 2 Guide Cath Balloon
	Final Pass Guide Cath Balloon
	Pass 1 Guide Cath Asp
	Pass 2 Guide Cath Asp
	Final Pass Guide Cath Asp
	Pass 1 Inter Cath Asp
	Pass 2 Inter Cath Asp
	Final Pass Inter Cath Asp
	Pass 1 Inter Cath Used
	Pass 2 Inter Cath Used
	Final Pass Inter Cath Used
	Pass 1 Int Cath Other:
	Pass 2 Int Cath Other:
Evaluation (continued)	Final Pass Int Cath Other:
	Pass 1 Distal Dev Trtmt App
	Pass 2 Distal Dev Trtmt App
	Final Pass Distal Dev Trtmt App
	Pass 1 DD Treat App Other
	Pass 2 DD Treat App Other

	Final Pass DD Treat App Other
	Pass 1 Stent Retriever
	Pass 2 Stent Retriever
	Final Pass Stent Retriever
	Pass 1 Stent Rtrvr Other
	Pass 2 Stent Rtrvr Other
	Final Pass Stent Rtrvr Other
	Pass 1 Stent Ret Dia
	Pass 2 Stent Ret Dia
Outcomes	Hemorrhagic Infarction (HI) 1
	HI2
	Parenchymal hematoma (PH) 1 Type Hemorrhagic Transformation
	PH2 Type Hemorrhagic Transformation
	Parenchymal hematoma remote from infarcted brain tissue
	Intraventricular hemorrhage
	Subarachnoid hemorrhage
	Subdural hemorrhage
	Please Specify:
	Discharge Date
	Discharge Status
	Date of Death
	Post-Operative Length of Stay
	Alive at 24 Hours?
	24 Hour National Institute of Health Stroke Score
	24 Hour Computerized Tomography
	Date of Contact
	Contact By
	Current Living Status; (Rehab, Nursing Facility, Hospice, Home, Dead)
	Date of Death
	Cause of Death
	Current Smoking
	30 Day Modified Rankin Score
	30 Day National Institute of Health Stroke Score
Outcomes (continued)	Re-admission within 30 days
	90 Day mRS
	90 Day NIHSS
	Re-admission within 90 days
	1 Year mRS

SPARED CRN

The following table includes the minimum core data elements that are identified:

Table 8: SPARED Minimum core data elements

Clinical Workflow	Data Element
Patient Information	Record ID
	Patient Initials
	Patient Date of Birth
	Social Security Number
	Race
	Hispanic/Latino Ethnicity
	Patient Email
	Enrolling Center
	Date of Research Consent
	Consented By
	Height
	Weight
	Comorbidities
	Prior Prostate Cancer Treatments
Evaluation	Pre-ablation PSA Date
	Pre-ablation PSA Value
	Pre-ablation PSA on dutasteride or finasteride
	Date of Pre-ablation Biopsy
	Type of Biopsy Performed
	Type of MRI Fusion
	Total Number of Systematic Cores Taken
	Total Number of Positive Systematic Cores
	Total Number of MRI Targets Biopsied
	Total Number of Positive MRI Targets
	Highest ISUP Grade Group Within the Ablated Volume
	Highest ISUP Grade Group Outside the Ablated Volume
	Pre-ablation T stage
	Pre-ablation N stage
	Pre-ablation M stage
	Pre-ablation mpMRI Performed
	Date of Pre-ablation mpMRI
	Pre-ablation prostate volume on mpMRI
	Highest PI-RADS v2 Grade Lesion Within the Ablated Volume on Pre-ablation mpMRI
	Number of PI-RADSv2 3-5 Lesions Within the Ablated Volume on Pre-ablation mpMRI
	Highest PI-RADS v2 Grade Lesion Outside the Ablated Volume on Pre-ablation mpMRI

	Number of PI-RADSv2 3-5 Lesions Outside the Ablated Volume on Pre-ablation mpMRI
	Total Number of Positive MRI Targets
Management	Duration of Active Surveillance
	Duration of Androgen Deprivation
	Date of Last Dose of Androgen Deprivation
	Date of Prior Brachytherapy
	Date of Prior Ablative Therapy
	Start Date of Prior Radiation Therapy
	End Date of Prior Radiation Therapy
	Total Delivered Dose of Prior Radiation Therapy
	Pattern of Prior Ablative Therapy
	Details of Prior Ablative Therapy
	Date of Ablation Procedure
	Surgeon Name
	Treating Center
	Outlet Procedure Performed Prior to Ablation?
	Date of Outlet Procedure
	Type of Outlet Procedure
	Type of Anesthesia During Ablation
	Ablation Device Used
	If other, what device?
	Ablation Pattern
	Image-Guidance During Ablation
	Cancer Intentionally Omitted from Treatment
	Highest Grade Group of Omitted Cancer
	Time to Complete the Ablation (minutes)
	Volume of Ablation
Outcomes	Intraoperative device related complication or malfunction?
	If yes, please describe
	Date of EPIC questionnaire completion
	Overall, how much of a problem has your urinary function been for you?
	Which of the following best describes your urinary control?
	How many pads or adult diapers per day have you been using for urinary leakage?
	How big a problem, if any, has urinary dripping or leakage been for you?
	Pain or burning with urination
	Weak urine stream/incomplete bladder emptying
	Need to urinate frequently
	Current LUTS Medications
	Rectal pain or urgency of bowel movements
	Increased frequency of your bowel movements

	Overall problems with your bowel movements
	How do you rate your ability to reach orgasm (climax)?
	How would you describe the usual quality of your erections?
	Overall, how much of a problem has your sexual function or lack of sexual function been for you?
	Current Erectile Aids
	Hot flashes or breast tenderness / enlargement
	Feeling depressed
	Lack of Energy
	Date of SHIM questionnaire completion
	1. How do you rate your confidence that you could keep an erection?
	2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
	3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
	4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
	5. When you attempted sexual intercourse, how often was it satisfactory for you?
	Current Erectile Aids
	Date of IPSS questionnaire completion
	1. Incomplete Emptying - How often have you had the sensation of not emptying your bladder?
	2. Frequency - How often have you had to urinate less than every two hours?
	3. Intermittency - How often have you found you stopped and started again several times when you urinated?
	4. Urgency - How often have you found it difficult to postpone urination?
	5. Weak Stream - How often have you had a weak urinary stream?
	6. Straining - How often have you had to strain to start urination?
	7. Nocturia - How many times did you typically get up at night to urinate?
	QoL - If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?
	Current LUTS Medications
	Date of Adverse Event Assessment
	Has the patient experience any adverse events since the date of ablation or last follow-up?

	Date of Onset
	Adverse Event Description (CTCAEv5.0)
	Additional Description of the Adverse Event
	Action Taken
	Procedure, Hospitalization, or Other Details
	Grade (CTCAEv5.0)
	Outcome of Adverse Event
	Date of Resolution or Death
	Reason for PSA Check
	Reason for Concern
	Other Reason for Concern, provide details
	Post-ablation PSA Date
	Post-ablation PSA Value
	Post-ablation PSA on dutasteride or finasteride?
	Date of Biopsy
	Reason for Post-ablation Biopsy
	Reason for Concern
	Other Reason for Concern, provide details
	Type of Post-ablation Biopsy Performed
	Total number of cores
	Number of Positive cores
	Cancer Within the Ablated Volume on Post-ablation Biopsy
	Highest ISUP Grade Group Within the Ablated Volume on Post-ablation Biopsy
	Cancer Outside the Ablated Volume on Post-ablation Biopsy
	Highest ISUP Grade Group Outside the Ablated Volume on Post-ablation Biopsy
	Date of Post-ablation mpMRI
	Reason for Post-ablation mpMRI
	Reason for Concern
	Other Reason for Concern, provide details
	Post-ablation prostate volume on mpMRI
	Highest PI-RADS v2 Grade Lesion Within the Ablated Volume on Post-ablation mpMRI
	Number of PI-RADSv2 3-5 Lesions Within the Ablated Volume on Post-ablation mpMRI
	Highest PI-RADS v2 Grade Lesion Outside the Ablated Volume on Post-ablation mpMRI
	Number of PI-RADSv2 3-5 Lesions Outside the Ablated Volume on Post-ablation mpMRI
	Date of Last Follow-up
	Assessment at Last Follow-up

	Status at Last Follow-up
	Sites of Metastatic Disease
	Cause of Death
	Other Cause / Cancer ICD 10
	Subsequent Treatment
	Subsequent Treatment Details
	Indication for Subsequent Treatment
	Start Date of Subsequent Treatment
	End Date of Subsequent Treatment
	Intraoperative device related complication or malfunction?
	If yes, please describe
	Date of EPIC questionnaire completion
	Overall, how much of a problem has your urinary function been for you?
	Which of the following best describes your urinary control?
	How many pads or adult diapers per day have you been using for urinary leakage?
	How big a problem, if any, has urinary dripping or leakage been for you?
	Pain or burning with urination
	Weak urine stream/incomplete bladder emptying
	Need to urinate frequently
	Current LUTS Medications
	Rectal pain or urgency of bowel movements
	Increased frequency of your bowel movements
	Overall problems with your bowel movements
	How do you rate your ability to reach orgasm (climax)?
	How would you describe the usual quality of your erections?
	Overall, how much of a problem has your sexual function or lack of sexual function been for you?
	Current Erectile Aids
	Hot flashes or breast tenderness / enlargement
	Feeling depressed
	Lack of Energy
	Date of SHIM questionnaire completion
	1. How do you rate your confidence that you could keep an erection?
	2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?

	3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
	4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
	5. When you attempted sexual intercourse, how often was it satisfactory for you?
	Current Erectile Aids
	Date of IPSS questionnaire completion
	1. Incomplete Emptying - How often have you had the sensation of not emptying your bladder?
	2. Frequency - How often have you had to urinate less than every two hours?
	3. Intermittency - How often have you found you stopped and started again several times when you urinated?
	4. Urgency - How often have you found it difficult to postpone urination?
	5. Weak Stream - How often have you had a weak urinary stream?
	6. Straining - How often have you had to strain to start urination?
	7. Nocturia - How many times did you typically get up at night to urinate?
	QoL - If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?
	Current LUTS Medications
	Date of Adverse Event Assessment
	Has the patient experience any adverse events since the date of ablation or last follow-up?
	Date of Onset
	Adverse Event Description (CTCAEv5.0)
	Additional Description of the Adverse Event
	Action Taken
	Procedure, Hospitalization, or Other Details
	Grade (CTCAEv5.0)
	Outcome of Adverse Event
	Date of Resolution or Death
	Reason for PSA Check
	Reason for Concern
	Other Reason for Concern, provide details
	Post-ablation PSA Date
	Post-ablation PSA Value
	Post-ablation PSA on dutasteride or finasteride?
	Date of Biopsy

	Reason for Post-ablation Biopsy
	Reason for Concern
	Other Reason for Concern, provide details
	Type of Post-ablation Biopsy Performed
	Total number of cores
	Number of Positive cores
	Cancer Within the Ablated Volume on Post-ablation Biopsy
	Highest ISUP Grade Group Within the Ablated Volume on Post-ablation Biopsy
	Cancer Outside the Ablated Volume on Post-ablation Biopsy
	Highest ISUP Grade Group Outside the Ablated Volume on Post-ablation Biopsy
	Date of Post-ablation mpMRI
	Reason for Post-ablation mpMRI
	Reason for Concern
	Other Reason for Concern, provide details
	Post-ablation prostate volume on mpMRI
	Highest PI-RADS v2 Grade Lesion Within the Ablated Volume on Post-ablation mpMRI
	Number of PI-RADSv2 3-5 Lesions Within the Ablated Volume on Post-ablation mpMRI
	Highest PI-RADS v2 Grade Lesion Outside the Ablated Volume on Post-ablation mpMRI
	Number of PI-RADSv2 3-5 Lesions Outside the Ablated Volume on Post-ablation mpMRI
	Date of Last Follow-up
	Assessment at Last Follow-up
	Status at Last Follow-up
	Sites of Metastatic Disease
	Cause of Death
	Other Cause / Cancer ICD 10
	Subsequent Treatment
	Subsequent Treatment Details
	Indication for Subsequent Treatment
	Start Date of Subsequent Treatment
	End Date of Subsequent Treatment

TMJ CRN

The following table includes the minimum core data elements that are identified:

Table 9: TMJ Minimum core data elements

Clinical Workflow	Data Element
Patient Information	Last Name
	First name
	Date of birth
	Sex
	Gender
	Employment status
	Disability status
	Race
	Ethnicity
	State of residence
	Country
	E-mail address
Provider Information	Capturing provider related information
	Capturing additional information about patient care to provider
	Granting or removing access to data to provider (Y/N)
	Provider type
	Provider organization
	Last name
	First name
	Address
	Street number and name
	City
	State
	Zip code
	Phone
	Email address
Evaluation	Usage of the prescription medications, over the counter, supplements, herbals (including cannabis)
	Any Chemotherapy received
	Any Therapeutics Radiation/Radiotherapy received **Note: Should leverage how this is collected in other registries*
	Unique Device Identifier (UDI) available on the implant card
	Device Type
	Manufacturer
	Brand Name
	Device Model
	Any known common allergies
	Metal allergies
	Medication allergies

	Reasons seeking care captured by clinicians (Y/N)
	Symptom Details - Onset (sudden or gradual)
	Symptom Details - Laterality
	Symptom Details - Severity
	Symptom Details – Duration*
	Symptom Type - Symptoms in the Jaw You would be asked to select one or more the following choices: fatigue in your jaw when talking and/or chewing, stiffness in your jaw, clicking with or without pain, popping, cracking, crepitus grating, squishy/fluid sound, squeaking (TMJ Implant patients only), Eustachian tube dysfunction/ear clicking sounds/fullness in the ear, other
	Symptom Type - Symptoms in the mouth and tongue You would be asked to select one or more the following choices: difficulty opening and closing, pain/difficulty to close mouth, pain/difficulty to open mouth, tongue thrusting, mouth breathing, difficulty swallowing, pain while swallowing, gross motor control, fine motor control, difficulty chewing, dietary restrictions related to chewing, lack of taste, distortion of taste, other
	Symptom Type - Symptoms in the eyes You would be asked to select one or more the following choices: pain behind your eye(s), vision correction, blurry vision, other
	Symptom Type - Symptoms in the ears You would be asked to select one or more the following choices: earaches, fullness or ringing in your ears, Eustachian tube dysfunction, Fluid/drainage from ear, ear tubes, other
	Symptom Type- Headaches You would be asked to select one or more the following choices: Cluster headache, Migraine headache, Sinus headache, Tension headache, Fogginess, other
	Symptom Type - Sleep problem or disorder You would be asked to select one or more the following choices: insomnia (inability to fall asleep), obstructive sleep apnea (airway is blocked), central sleep apnea (airway is not blocked), complex/mixed sleep apnea syndrome, other
	Symptom Type - Symptom Triggers You would be asked to select one or more the following

	choices: eating, yawning, crying, weather, mask wearing, poor sleep/position, prolonged sitting, talking, posture, coughing/sneezing, stress, dental x-rays, other Medicap procedures/testing, other
	Coronary Artery Disease
	Artificial Heart Valve
	Congenital Heart Defect
	Heart Murmur
	High blood pressure
	Low blood pressure
	Infective Endocarditis
	Mitral Valve Prolapse
	Rheumatic Fever
	Abnormal Heart Rhythm
	Raynaud's Phenomenon
	Vasculitis
	Aneurysm
	Postural Orthostatic Tachycardia Syndrome (POTS)
	Headaches
	Chronic fatigue syndrome
	Tooth Deterioration - missing, damaged/cracked, caries (tooth decay), dry socket, loose, root resorption
	Frenulum developed from scar tissue
	Gum Recession
	Adrenal Disorders
	Diabetes
	Thyroid Disorders
	Sexual Dysfunction
	Hormone disorders (e.g., PCOS, Infertility, male hormone disorders, female hormone disorders)
	Menopause
	Painful Menstrual Periods
	Endometriosis
	Premenstrual Syndrome (PMS)
	Estrogen-based Hormone Replacement Therapy (including hormonal birth control)
	Salivary stone
	Sinusitis
	Clenching and Bruxism
	Past medical history - Ophthalmology and vision acuity (Y/N)
	Acid Reflux/GERD/Heartburn/hiatal hernia
	Ulcerative Colitis/ Crohn’s
	Gastritis
	Intestinal/Stomach Ulcers

	Irritable Bowel Syndrome
	Malnutrition, weight fluctuation
	Liver disease/Jaundice/Hepatitis
	Pancreatic disease
	Bladder infections/ bladder dysfunction/incontinence
	Interstitial Cystitis
	Prostatitis
	Nephroptosis
	Urolithiasis
	Chronic Pyelonephritis
	Testicular Tumors/Disorders
	Vulvar vestibulitis syndrome/vulvodynia
	Anemia
	Chronic swollen Lymph Nodes
	Hemophilia
	Blood transfusion
	Sexually Transmitted Disease
	Lyme/Tick/or insect borne diseases or infections
	MRSA or other chronic infection (staph, strep)
	Arthritis - Infectious
	Epstein–Barr virus (EBV)
	Osteoporosis
	Metabolic bone disease, bone remodeling
	Muscular Dystrophy
	Osteochondritis dissecans
	Eagle Syndrome
	Fibromyalgia
	Congenital/Craniofacial Disorders (e.g., Hemifacial Microsomia/Goldenhar Syndrome, hyperplasia etc.)
	Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ)
	Medication-related osteonecrosis of the jaw (MRONJ)
	Ehlers-Danlos syndrome (EDS) or 'collagen' problems, connective tissue disorder
	Avascular Necrosis of temporomandibular joint*
	Eyebrow/Eyelid/Facial paralysis & Numbness
	Bell's Palsy
	Burning Mouth Syndrome, burning tongue
	Cerebral palsy
	Epilepsy/Seizures/Convulsions
	Ernest Syndrome
	First bite syndrome/ Frey Syndrome
	Sleep Disorders/Fatigue /Obstructive Sleep Apnea/ Central Sleep apnea

	Movement Disorders/ Oromandibular dystonia/dystonic tremor/cervical dystonia
	Trigeminal Neuralgia (pain in the nerve)
	Trigeminal Neuropathy (pathology of the nerve - e.g., pain or weakness - can cause neuralgia)
	Vertigo/ dizziness/ spaciness
	Multiple Sclerosis
	Migraine, Cluster, tension, Premenstrual migraine
	Myasthenia Gravis
	Stroke
	Trigeminocardiac reflex
	Traumatic injury to the head or neck
	Oncology history (e.g., Cancer of Bone, Breast, GI, Leukemia, Lymphoma, Lung, Prostate, Mandibular, oral)
	Conditions affecting the Lungs/Pulmonary (e.g., asthma)
	Reproductive history/past pregnancy history (e.g., number of pregnancies and live births)
	Arthritis - Traumatic
	Arthritis - Rheumatoid
	Arthritis - Osteoarthritis/Degenerative
	Arthritis - Psoriatic
	Arthritis - Gouty
	Arthritis - Seronegative
	Mast Cell Activation Syndrome (MCAS)
	Misdiagnosis of TMD (mimics)
	Use of Tobacco/ Vaping
	Tobacco/ Vaping Usage information (e.g., use tobacco to manage TMD pain, smoke tobacco, chew tobacco, vape, other)
	Use of Alcohol products
	Alcohol usage information (e.g., use alcohol beverages to manage TMD pain, drink once a month, drink once a week, drink multiple times a week, drink daily, other (specify)
	Use of Recreational Drugs
	Recreational Drugs Usage information (e.g., use recreational drugs to manage TMJ pain, use once a month, use once a week, use multiple times a week, daily use)
	Family history of TMJ/D (Y/N)
	Consultation with a medical or dental specialist for TMJ/D
	Type of specialist
	Information about the specialist (e.g., name or providers)
	Pre TMJ implant information about the patient's TMJ condition prior to TMJ implant

	Post TMJ implant information about the patient's TMJ condition after a TMJ implant
	Previous TMJ/TMD Treatment
	Time from symptom onset to diagnosis of previous Treatment
	Steroid injections
	PRP injections
	Prolotherapy/ Trigger Point injections/nerve blocks
	Botox Injections
	Iontophoresis with Dexamethasone, lidocaine, benzocaine, septocaine and/or others
	Massage Therapy
	Cranial Sacral Therapy
	Myofascial & Precision Neuromuscular massage therapy
	Therapeutic exercises (posture and mechanical training)
	Manual Therapy
	Acupuncture/Dry needling
	Myofunctional/Speech Therapy
	Physical Therapy/Physiotherapy
	Chiropractic Treatment
	IV Ozone
	Shock wave therapy
	Hyperbaric oxygen therapy
	Cold laser therapy
	Ultrasound therapy
	Magnetic therapy
	Heat therapy
	Breath Work
	Physical Rehabilitation
	Splint/ orthotic/ mouth guard/ night guard (Custom vs OTC)
	Education/Counseling/Training Behavioral Therapy/Counseling (biofeedback, CBT, Relaxation training, hypnosis, stress management, mindfulness)
	Arthrocentesis
	Arthroplasty
	Arthroscopy
	Orthognathic surgery
	Total Joint Replacement (TJR)
	Joint Replacement for Tumor, Trauma, Others with Vascular/Bone Fibula Grafts
	Intraoral Vertical Ramus Osteotomy and Intermaxillary Fixation
	Date of previous TMD Surgical procedures
	Type of previous TMD Surgical procedures

	Previously failed surgeries ** Rephrase as: Surgery or procedure addressed or fixed the patient's problem (if not, provide additional information)*
	Number/type of surgical treatments (to be calculated by the entries)
	Autogenous Reconstruction
	Condylectomy/ Condylotomy (spacer used)
	Discectomy/Reconstruction/Repair
	Disc replacement (material, Silastic, fat, temporalis flap)
	Failed non-surgical procedure
	Wisdom tooth extraction complication
	Myofascial & Precision Neuromuscular treatment, muscular electrical stimulation (TENS)
	Manipulation of mandible
	Brand name
	Generic name
	Drug class
	Brand name
	Generic name
	Drug class
	Descriptive diagnosis of patient visit captured by clinician
	Jaw Function/Dysfunction ** Consider the following assessment tool: JFLS-SF*
	Diet
	Pain onset
	Pain quality
	Pain duration
	Angle's Classification
	Wilkes Staging Classification for Internal Derangement ** Note: Optional for specialist clinicians only*
	Charlson comorbidity Index ** Note: To automated, include the overlap vs. missing conditions in past medical history. This is a ten year mortality predictor.*
	Malocclusion ** Note: Revise to "occlusion" with the following response options: class 1,2 (div 1 or 2) ,3 and AOB, lateral open bite, scissor bite. This can be incorporated int the Angle's classification.*
	Deviated opening laterality, mm from midline ** Note: Allow options of deviation or no deviation, and laterality instead of measure in mm from midline.*

	General condition of dentition (e.g., tooth wear, decay, etc.) ** Note: Expand the value set to include: Tooth wear or cracked/fractured/broken (Incisal, Cuspid, Bicuspid, Molars)*
	Maximum Interincisal Opening ** Note: Include additional information: With Pain, Without Pain, Assisted or Unassisted*
	Range of Motion (ROM) ** Note: Include Excursive Movement*
	Facial asymmetry ** Note: Include the following response options: temporalis, masseter hypertrophy and atrophy, chin point deviation, other/specify*
	Examination of temporalis tendon
	Pressure pain threshold
	Diagnosis based on clinical assessment (Y/N)
	Clinician Identifier
	Type of Clinician
	Facility Identifier
	C-Reactive Protein (CRP) Test
	Complete Blood Count (CBC) Test
	Rheumatoid Factor (RF) Test
	Erythrocyte Sedimentation Rate (ESR) Test
	Immunofluorescent ANA with reflex ENA Test
	Anti-CCP antibodies
	CT Scan with or without contrast
	Magnetic Resonance Imaging (MRI) findings
	Panoramic findings
	Other Imaging (identify)
	Clinical assessment - TMJ/D specific diagnostics test
Management	Date of Procedure
	Procedure Code
	Interventional Site (body location)
	Procedure Status (e.g., Completed, Treatment Aborted, Incomplete)
	Procedure Urgency (e.g., Elective, Urgent, Emergency)
	Facility (location)
	Surgeon(s) performing the procedure
	Length of Procedure
	Anesthesia Type
	Device Details – Single Needle Gauge
	Device Details – Double Needle Gauge
	Device Details – Small Diameter Arthroscopy (1MM) Type

	Procedure Details – Complications
	Procedure Details – Additional Procedures Needed
	Anesthesia Type
	Single Portal
	Double Portal
	Triple Portal
	Level 1
	Level 2
	Level 3
	Biopsy Required
	Fluid Analysis
	Lavage Type
	Lavage Amount
	Medication Type
	Medication Amount
	Complications
	Use of Laser
	Additional Procedures Needed
	Anesthesia Type
	Prep and Drape
	Incision Type
	Soft Tissue Debridement
	Disc Displacement Reduction and Fixation
	Meniscectomy
	Hard Tissue Reduction and Contouring: Condyle
	Hard Tissue Reduction and Contouring Fossa/Eminence
	Temporalis Flap Interposition
	Fat Graft Interposition
	Spacer Synthetic Temporary Material joint
	Complications
	Additional Procedures Needed
	Anesthesia
	Prep and Drape
	UDI Stock TMJ TJR
	UDI Custom TMJ TJR
	Incisions Type
	Incisions Position ** Note: Combine with Incision Type*
	Fat Graft
	Bone Cement
	Fossa Component/Screws
	Mandible Component/Screws

	Complications
	Operation Changed from Custom to Stock TJR
	Additional Procedures Needed
	Anesthesia
	Prep and Drape
	Extra Oral
	Intra-Oral
	With TJR
	Removal of Coronoid Process In Toto
	Leave Part of The Coronoid Process Attached To Temporalis Muscle
	Complications
	Additional Procedures Needed
	Anesthesia
	Prep And Drape
	Maxilla Surgery
	Mandible Surgery and Splints
	Maxilla And Mandible Surgery
	Turbinectomies
	Total Joint Replacement
	Complications: Bleeding, Control Of Bleeding
	Additional Procedures Needed
	Anesthesia
	Prep And Drape
	Resection Of Tumor Or Bony Fracture Per Protocol
	Harvest Of Vascular/Bony Fibula Graft
	Reconstruction Of TMJ/Fossa/Mandible With Fibula Graft
	Fibula Grafts Complications
	Additional Procedures Needed
	Anesthesia
	Prep And Drape
	Intermaxillary Fixation
	Complications: Bleeding, Control Of Bleeding, Other
	Additional Procedures Needed
	Device UDI
	Device type
	Device class
	DI number
	Company Name
	Brand Name
	Model Number
	Implant material
	Dose

	Dose Units
	Code
	Type Class
	Start Date
	End Date
Outcomes	Open Bite
	Range of Motion (ROM)
	Crossbite
	Overjet
	Deviated Opening
	Device integration with bone or soft tissue
	Infection e.g., biofilm infection, others?
	Device Removal (including details about the device or surgical site)
	Device Failure (including damage to device or device component)
	Complications occurring during removal procedure
	Change in disability status after procedure
	Reoperations
	Lost to Follow-up and Lost to follow-up Type
	Readmission and Date
	Chronic lymphocytic infiltrate present
	Mortality – Date of death
	Mortality – Cause of death
	EuroQoL five dimension (EQ-5D-5L) (Pre-Op to 60 months)
	Jaw Function limitation scale 8 – (Pre-Op, 3 months, 12 months)
	OHIP-TMD (Pre-Op to 60 months)
	Pain Numeric Rating Scale (NRS) (Pre-Op to 60 months)
	SF-12 (Pre-Op, 3 months, 12 months) *Note: These were also evaluated by the TMD PROMs Working Group and will be addressed in their recommendation*
	Chronic lymphocytic infiltrate present
	Mortality – Date of death
	Mortality – Cause of death
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	Jaw Function limitation scale 8 – (Pre-Op, 3 months, 12 months)
	OHIP-TMD (Pre-Op to 60 months)
	Pain Numeric Rating Scale (NRS) (Pre-Op to 60 months)

	SF-12 (Pre-Op, 3 months, 12 months) *Note: These were also evaluated by the TMD PROMs Working Group and will be addressed in their recommendation*

VANGUARD CRN

The following table includes the minimum core data elements that are identified:

Table 10: VANGUARD Minimum core data elements

Clinical Workflow	Data Element
Patient Information	Patient identifier
	Ethnicity
	Gender
	Race
Evaluation	Provider Name
	Provider Role
	Attending Service
	Admission status
	ICD-10 diagnosis
	Indication
	Risk factors
	History of difficult access
	History of prior venous catheter-related infection
	Provider Name
	Provider Role
	Attending Service
	Admission status
	ICD-10 diagnosis
	Indication
Management	VANGUARD classification of venous obstruction (above diaphragm)
	VANGUARD classification of venous obstruction (below diaphragm)
	Insertion date
	Location of insertion procedure
	Vein Selected for Access - Side
	Vein Selected for Access - Location
	CVAD Device (UDI)
	Catheter Tip position - Tip position in vertebral body units above or below the carina
	Prophylactic antibiotic/medication?
	Evaluation of technical success

	Physician service responsible for longitudinal venous access device surveillance
	Clinician title completing current report (if other than responsible clinician)
	Immune status
	Patient temperature, maximum over prior 24 hours
	Abnormal temperature since last report, (degrees Celsius)
	Were rigors (shaking chills) reported
	Was abnormal blood pressure reported
	Record lowest systolic blood pressure over past 24 hours
	Was abnormal white cell count reported
	Was abnormal differential reported
	Drainage/discharge at insertion site, along catheter tract, or at port pocket since last report
	Access events per catheter per day
Outcomes	Complication date
	Date of device removal (insertion site abandoned, select reason below)
	Date of device salvage (insertion site maintained, select reason below)
	Cultured organism(s)
	Culture source, method and results (date & result each occurrence)
	Swab
	Catheter tip culture (Maki method)
	Port hub culture
	Peripheral blood culture
	Blood culture through catheter
	Differential time to positivity
	Exit site infection
	Tunnel infection
	Pocket infection
	Wound infection
	Catheter related bloodstream infection
	Sepsis of unknown origin, probably catheter-related
	Sepsis of unknown origin, probably not catheter-related
	End of therapy (endpoint achieved, no evidence of catheter failure)
	Catheter exchange over a guide wire
	Antibiotic therapy (each use)
	Agent
	Date

	Dose
	Dose unit
	Clinical endpoint definition