Recommendations for a National Medical Device Evaluation System

Strategically Coordinated Registry Networks to Bridge Clinical Care and Research

A Report from the Medical Device Registry Task Force
& the Medical Devices Epidemiology Network

DRAFT FOR PUBLIC COMMENT

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Contents

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About the Medical Device Epidemiology Network Public-Private Partnership

The mission of the MDEpiNet Public-Private Partnership (PPP) (http://mdepinet.org) is to develop and maintain national and international scientific infrastructure and methodologic approaches to overcome and eliminate discontinuities in device evaluation and surveillance that currently exist within the total product life cycle. In support of this mission the PPP engages a broad base of stakeholders across the medical device innovation ecosystem through its operational committees and activities. MDEpiNet PPP promotes a collaborative, pre-competitive focus on novel, more efficient and more informative approaches to device benefit/risk and safety surveillance challenges through think-tank programs, publications and disease specific/device specific working groups and research projects.

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None.

Executive Summary

In June 2014 two parallel groups were tasked with providing recommendations to FDA toward development of a national medical device system that could both support better regulatory decisions and serve stakeholders across the medical device innovation ecosystem. Planning Board recommendations coordinated through the Brookings Institution were shared publicly in February 2015. The Medical Device Registries Task Force (MDRTF) was convened through the Medical Device Epidemiology Network Public Private Partnership to focus on the objectives, operations and architecture of such a system. This report constitutes the MDRTF recommendations.

The spirit of these recommendations is not that of a completed National System proposal—in fact many additional questions are crystallized by these recommendations, an inevitability at this stage of planning something so novel in an arena as diverse as that of medical devices. The spirit of these recommendations is to complement and extend many of the Planning Board perspectives with additional, pragmatic considerations that could help define immediate next steps for system development and launch. Central to these recommendations is the focus on a scalable system architecture supporting a staged implementation of the National System, beginning in selected priority device areas. Emphasis is placed on a central, public domain cataloguing of approaches to partnering, governance, data sharing and dissemination of stakeholder-oriented deliverables, incentivizing the re-use these early lessons learned and successful interoperability solutions as the System expands to further medical device areas. The principle tool of this approach is a portfolio of pilot projects that have both immediate impact on specific device-related issues and that provide predicates for more generalizable principles that can be applied in other device areas. This implementation strategy promotes a National System that cultivates internal consistency and accelerates startup areas while preserving flexibility for customization to both specific devices and to individual stakeholder needs. Combining consistency and flexibility in architecture is considered one of the most fundamental recommendations of the MDRTF, as over time the National System must also accommodate the pace of new, emerging electronic health information systems. Thus the Task Force does not recommend building a National System de novo, as even if the funding necessary was allocated, the system would be outdated by the time it was ready for implementation.

Clarifying the core objective of the National System was also considered a foundational area of recommendations. To this end the Task Force emphasizes an integrated shift in both infrastructure and analytic methodologies related to medical device data that would fill current gaps in device evaluation and promote continuous accrual of benefit/risk and safety knowledge from invention to obsolescence—the original intention of the total product life cycle (TPLC) construct. Notably this construct applies not only to the life cycle of a single device, but over the maturation of a device space through the development of multiple device iterations in the competitive marketplace. Deliverables from the National System should include better, more efficient regulatory science-based decisions in conjunction with device information dissemination customized to stakeholder groups, including patients, clinicians, professional

societies, regulators, manufacturers, payers and others with currently unanswered questions about outcomes or comparative effectiveness of a particular brand or model of a device in real world use.

To achieve this core objective, the MDRTF defined the key recommendations for system architecture according to their pragmatic and operational ability to support critical changes in methodologic approaches advancing device benefit/risk and safety signal analytics. Currently, medical device data arise from disparate data sources with variable data elements, data definitions, data quality, and frequently from only limited subsets of patient exposures. Contemporary methodologies applied to compilations of information from such sources expend computational and statistical power overcoming the source data's idiosyncratic heterogeneity, e.g., filtering chance noise from real outcomes, benefits or safety signals. Historically to move beyond such noise discrimination became the arena of dedicated clinical trials research systems, including the often de novo construction of singular clinical trial case report forms, infrastructure and operations at great cost. In this setting research study designs often use reductionist inclusion/exclusion criteria and selected participating centers, leaving important residual questions on the generalizability of study findings. While enhancing specific device evaluation questions in defined populations, most often this expensive and time consuming approach leaves a substantial gap between clinical research data and actual outcomes encountered in real world clinical practice.

The National System envisioned by the Medical Device Registry Task Force (MDRTF) changes this analytical paradigm through emphasis on the development of strategically partnered electronic health information systems that support both 1) the implementation of structured device identifiers, core minimum data elements and definitions, and 2) the ability to share complementary data across information systems. The Task Force refers to these partnered complementary systems as strategically "Coordinated Registry Networks" or CRNs.

As envisioned by the MDRTF, as CRNs deliver wider patient access using device identification and more structured data specific to questions of device evaluation, a systematic shift from current idiosyncratic heterogeneity to the capture of the genuine heterogeneity of clinical practice is cultivated. Commensurate with this shift, the unique device, the procedure, operator proficiency, patient characteristics, hospital or regional clustering and clinical outcomes assume statistically assignable dimensionality. Methodologies applied to compilations of such CRN information could be far more informative as to whether it is a particular device design, operator training, patient selection or combinations that actually drive clinical benefits, safety signals and health care expenditures. In this model, the substrate of clinical practice and clinical research are incorporated into a single body of highly informative and accessible data, promoting more efficient and continuously updated and enhanced knowledge capable of supporting better regulatory decisions, reimbursement decisions, best practice recommendations, patient information and innovation opportunities for manufacturers.

Such a shift from idiosyncratic data heterogeneity to clinical practice dimensionality implies false safety signals are less likely and true safety signals could be detected earlier and with greater precision. This could mean less harm to patients as well as the transformation from current amorphous safety signals that primarily cause public unease to safety signals that provide precision engineering targets for new generation devices. Conjoined with more efficient structured data accrual pathways, safety signals in a CRN-based system could profoundly inform and even incentivize early feasibility and pivotal pre-market evaluations of novel device designs—a true TPLC impact—where currently safety signal detection often adds burden to further device innovation. With this core objective of advancing both the quality and the efficiency of evidence collection supporting TPLC regulatory decisions, best practice recommendations, patient updates and information, and payer decisions, the Task Force recommends renaming the system from a "surveillance" system to the National Medical Device Evaluation System.

Task Force recommendations for CRN architecture, and thus for the National System, center on leveraging existing, self-sustaining electronic resources, such as device registries, electronic health records, administrative data and even social media and personal mobile device sources. MDRTF included two broad perspectives across its recommendations for this architecture: operational considerations and conceptual considerations.

Operationally, existing health information systems such as registries, health records and administrative data may already have governance processes, widespread implementation, established integration into clinical workflow, and may already use standardized data elements and definitions. "Dual purposing" such information systems as components of CRNs reduces re-engineering, beta-testing, staff training and numerous additional cost- and time-sensitive barriers to implementation toward device evaluation applications.

Conceptually, the Task Force recognized that while no single, standalone electronic health information resource currently exists that is sufficient for all device evaluation needs, data-sharing solutions between complementary electronic information sources could leverage strengths and overcome limitations of the individual participating components. Such linked or extracted data composites could provide high quality, patient level, device specific, highly informative composite data sets far beyond any single electronic health information source. Of all current electronic information sources, the Task Force recognizes that medical device registries provide the most widely installed and singularly informative core elements for such composites, hence the nomenclature strategically coordinated "registry" networks (CRNs), even while acknowledging that key participating elements of a CRN may not be registries per se (e.g. electronic health records (EHRs), claims data, etc).

CRN architecture creating strategic data sharing interoperability across complementary health information systems thus also serves both the operational (internal consistency and flexibility) and conceptual (shift from idiosyncratic heterogeneity to assignable dimensionality) objectives of the National System. It supports staged implementation, customized initially to priority

device areas, generating lessons learned and data portability solutions that can be catalogued and re-used for consistency in other device areas as the National System grows. It also conveys an extremely flexible informatics foundation for the National System in the modern era where information technology is one of the fastest moving areas of new development—for instance it is quite conceivable that in a fairly modest period of time, electronic registries may be supplanted by health records as the most efficient and universal source of structured data for particular CRNs.

MDRTF recommendations on sustainability and governance note that partnering and integration of independent systems is easy to conceive, as are business models that could assign segmented costs to areas of work and deliverables, however in the current medical device landscape of fragmentation and distrust, no amount of funding could guarantee success of a National System. Conversely, the Task Force recognized that, with transformation of the current landscape into one of good will and trust, the actual timelines and cost of doing business could be substantially mitigated through partnered CRN architecture (existing systems, dual purposing, etc). Early, successful implementation steps and deliverables could provide further evidence of and confidence in the value added of this pre-competitive collaborative approach, adding momentum to the organic growth the National System's CRNs across an expanding portfolio of device areas. Thus, for the National System and CRN architecture to succeed, the MDRTF recommendations emphasize the critical need to develop an internal agency to actively pursue the cultivation of partnering and good will. No one stakeholder alone can improve the quality and efficiency of device evaluation compared to what can be done working together. Owners of electronic health information systems will need to perceive CRN participation as an inclusive, even incentivized source of new opportunities, not as a loss of independence or source of added cost or work on behalf of others. Manufacturers will need to perceive the added speed and quality of CRN-based regulatory and reimbursement decisions throughout the TPLC as productive business models and incentives to innovation. Patients will need to perceive engagement, transparency and enhanced delivery of customized device information through the CRNs and National System as an incentive to allowing their personal health information to be included in ongoing device evaluations. The sustainability of the National System will not be based on fiscal cost, but on its ability to demonstrate that stakeholders working together with trust and good will provides a novel health care resource of priceless value.

Finally, in both its operational and conceptual objectives, the Task Force recognizes and encourages the suitability of a CRN-based National Medical Device Evaluation System to take further advantage of its architectural flexibility, emphasis on implementation of standardized, structured data and data portability solutions to align with and engage similar efforts in other areas. Such areas should include disease-based and other health information systems emerging outside of medical devices per se, as well as multi-lateral international efforts moving along these lines with global scope.

Preface

Redefining Health Care Culture, Not Just Systems; Providing Priceless Value, Not Just Mitigating Cost

Over more than a decade the importance and impact of electronic information to public health in the United States has progressed to national visibility across political parties and two administrations. From the January 2004 initiative launched by President Bush through President Obama signing the Health Information Technology for Economic and Clinical Health (HITECH) act into law in 2009 and the eventuation of Meaningful Use in the Patient Protection & Affordable Care Act, EHRs have been envisioned as health systems instruments that could help avoid medical errors, reduce costs, improve care, and save lives.

> *"If you want to go fast, go alone. If you want to go far, go together."*
>
> —African Proverb

Ironically, over that same period it could be argued that it took a major economic recession to expand this largely clinically focused vision to issues relating to clinical research applications leveraging electronic health information. Federal stimulus packages provided critical financial fuel, and a universal target rapidly emerged: eliminating unnecessary redundancy and fragmentation endemic in contemporary processes for testing and developing evidence to support decisions on new therapeutics coming to market as well as to their postmarket safety surveillance. Particularly for medical devices, such redundancy contributes nothing to the quality of device evaluation decisions while adding cost, delays and uncertainty to research and development pathways. As regulators and other federal agencies, manufacturers, hospitals, clinicians and investigators all wrestled with the fragmented and siloed traditional research world in the midst of draconian fiscal constraint, a corollary recognition emerged together with the focus on operationalizing less redundant systems: that willingness to work together on pre-competitive issues promoted leveraged solutions that no single stakeholder could forge. And as public-private partnership (PPP) efforts developed to cultivate the dialogue and chemistry of trust needed to sustain the good will to work as partners on behalf of the public health, the "win-win-win" directions that emerged further amplified the

Key Perspectives for Emerging Health Systems & Medical Devices

- Eliminating redundancy and fragmentation in evaluative processes improves benefit/risk and safety information while eliminating uncertainty, costs and delays for better devices reaching bedside care.

- Health care and clinical research options are much more pragmatic and more fruitful when stakeholders work together than when we work separately

simple message: health care and clinical research options are much more pragmatic and more fruitful when stakeholders work together than when we work separately.

In this environment, medical device evaluation concepts and systems all warrant timely review. A broad range of medical device technologies continue to emerge and iterate at a far more rapid pace than most pharma and biologics. Device evaluations often need unique information, such as device identifiers and operator proficiency. In such a complex and fast-moving universe, the need for a more efficient, partnered National System for device evaluation has been advanced by FDA's CDRH. The CDRH proposal for a National System is not simply for regulatory decision making and safety surveillance. Rather, the CDRH has encouraged development of a system positioned to help patients be more informed about their devices, to help manufacturers bring forward and improve devices more quickly and efficiently, to help practitioners define and refine best practice guidelines over time, to help guide payers to cost-effective technology—in other words, to promote a National Medical Device Evaluation System that serves as a national health care resource to all stakeholders in the medical device innovation ecosystem.

To help advise initial steps in developing both the vision and the execution of such a system, CDRH promoted several avenues for transparent, broadly based dialogue and recommendations. One of those avenues was the MDRTF. What follows is the report of that Task Force.

Over the course of its one year charter, the internal MDRTF dialogue progressed from an almost prohibitive and diffuse range of complex barriers facing the development of such a National System to a more manageable and even exciting focus on pathways that could be implemented and impactful in short-term timelines and with modest effort or investment—the "small steps to big changes" approach. Critical to the MDRTF recommendations is orchestration of both the operational and the partnering deliverables across these smaller efforts into foundational pieces supporting the longer term evolution of a better, more seamless, living, learning electronic healthcare system that ultimately could completely eliminate the traditional, artificial dichotomy between the needs of clinical practice and the needs of clinical research.

Small Steps to Big Changes

- Implement selected avenues that require only modest effort and investment and deliver impactful advances over brief timelines
- Orchestrate & catalogue both the operational and the partnering deliverables across these smaller efforts into foundational pieces supporting the longer term evolution of a better, more seamless, living, learning electronic healthcare system

One area of MDRTF focus was an opportunistic approach to leveraging high-quality device information that was already being gathered, and per its namesake one of the richest areas of such information is in electronic medical device registries. But not all high-priority devices have equally advanced registry infrastructures, and even for those that do it was quickly apparent that no single device registry could be sufficient for evaluating a device over the TPLC. On the

other hand, in many device areas the range of electronic data sources—not all of which are registries, but all electronic data repositories—could be strategically combined in "complementary" configurations so that each corrected deficiencies in the other. In this report, even though not every participating entity in such configurations is actually a registry per se, the construct is termed a strategically "coordinated registry network," or CRN.

Depending on the objectives (benefit/risk, safety surveillance, etc.) and the nature of the deficiencies to be corrected in configuring any particular device CRN—which include key factors ranging from device identification to duration of follow up to cohort access to ascertainment of outcome endpoints—a variety of interoperability/informatics solutions will be required at the systems operations level. The intrinsic flexibility of the CRN systems approach thus accommodates variations across specific priority devices and the extent to which mature registry infrastructure even exists for one device vs another.

A National System Built on Flexible, Strategically Coordinated Registry Networks (CRNs)

- Connecting "complementary" existing registries and electronic non-registry data sources (eg EHR, administrative data) each correcting the deficiencies of the other (device identifiers, operator proficiency, outcomes ascertainment, duration of follow up)
- Broad range of interoperability solutions for systems flexibility customized to device specific CRN objectives (eg. benefit/risk, safety surveillance) and available existing resource, if any (eg. existing registries, EHR data fields, standardized definitions)
- Evolution of a National System based on systems flexibility able to continuously adapt to both rapid changes in electronic modalities of health care data collection and the rapid pace of medical device innovation (eg. a learning National System)

At least as importantly, with the continuously accelerated pace of change across electronic health systems and IT infrastructure per se, the CRN approach solves the "one big system that will be outdated in 2 years" dilemma as well. Finally, this "centralized standards and essential principles" with decentralized operational flexibility also creates an intrinsically open architecture, open to other novel advancing areas of important device benefit/risk input such as from patients using smart phones, watches and other mobile or wearable technologies.

Another key focus of the Task Force, and perhaps most fundamental to its recommendations for a national medical device evaluative system, is the recognition that success of any national strategy will require good will and a genuine interest in partnering across stakeholders, agencies and organizations to actually make it work. This is critical not only for the systems solutions and efficiencies captured in the strategic CRNs structure, but also to enhance the sense of inclusiveness and participation across stakeholders in the structure and the objectives of the National System overall. With enhanced participation, the lingering distrust and exclusiveness so evident in our current medical device and health care culture can be profoundly altered. The shift from a culture of angst and distrust to a culture of good will and pre-competitive collaboration is the principal driver for a range of critical issues that will strongly impact the

momentum and even success of the National System's implementation. Such issues include patient willingness to provide informed consent or even allow their health data to be analyzed in research applications, and shifting postmarket safety signal detection from media-driven panic headlines to well defined targets for engineering of better, safer devices, in a system that not only is more sensitive to detection of safety signals, but that also most efficiently yields evidence of how new devices succeed in mitigating those signals.

The CRN structure, strategically integrating a variety of participating registries, health records and other data repositories relevant to a specific device class, also, in its very structure, opens a whole new range of avenues for encouraging stakeholder participation. As CRNs integrate their participating registries and other entities, the existing governance and advisory bodies of every local, regional, national and even international registry becomes stakeholder avenues for participation in the CRN. However, the Task Force clearly recognizes that for the potential of those avenues to be fulfilled, to be perceived as opportunities rather than to be perceived as an oppressive new layer of bureaucracy and governance—substantial and ongoing effort will need to be focused on engines and instruments actively fostering dialogue and good will. If we are to transform our traditionally separate and unequal device research and development landscape into a culture of collaboration and partnership on behalf of the national health we will be as obliged to actively provide this cultural solution as we are to providing systems interoperability solutions. And as with the systems-based solutions, successes at the CRN level will convey, as foundational elements, to the National System as well. The track record of PPPs along these lines represents perhaps the clearest such instrument available.

A Culture of Good Will & Partnering: The Biggest, Most Critical Challenge of All

- CRN and the National System must provide, and be perceived as providing, novel opportunities for stakeholder participation and registry/EHR dual purposing, not mandated bureaucratic loss of identity or governance
- Active, focused resources will be needed not only for systems solutions, but to transform current "separate and unequal" devices landscape to a culture of pre-competitive partnering and good will

Finally, the Task Force focused on issues of sustainability. The actual operational costs of maintaining and operating registries and data repositories, as well as the burden of populating them with data—work that most often falls on busy hospital staff and clinicians or onto patients themselves—are most opportunistically leveraged in strategic CRN structures whose participating entities are already fully operational, without additional cost or workload. This "dual purposing" of existing, operational participating entities significantly contributes to cost reductions and to the potential for this effort to be sustainable. However, the Task Force recognizes that financing and managing costs and workload alone are insufficient to developing a sustainable National System, even one built on existing sustainable registry or EHR entities. Rather, a system generated as part of a culture of partnered collaboration, inclusiveness and trust across stakeholders is what will produce a National System whose central analytic

capabilities defining device safety, benefit and risk can be delivered to individual stakeholders through means most customized to each stakeholder's perception of value. One system delivering to patients information that patients want and can understand; one system delivering to regulators robust profiles of benefit/risk and safety to support regulatory decisions; one system delivering to manufacturers precisely characterized performance targets, models of control populations, efficiency of data accrual and successful mitigation of previous safety signals; one system delivering to payers cost-effectiveness/comparative effectiveness metrics; one system, built through stakeholder good will and collaboration, providing value to all stakeholders, is what will fundamentally define the sustainability of the system as a national health care resource. It will not be the cost of the system. Rather it is a mandate that the value of the system will simply need to be "priceless" for healthcare.

Acronyms and Definitions

AAA	Abdominal aortic aneurysm
ACC	American College of Cardiology
AE	Adverse event
AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AJRR	American Joint Replacement Registry
API	Application-programming interface
BCBSA	Blue Cross and Blue Shield Association
BMS	Bare metal stents
CA	Catheter ablation
CABG	Coronary bypass graft
CART	Clinical Assessment Reporting and Tracking
CDRH	Center for Devices and Radiologic Health
CED	Coverage with Evidence Development
CER	Comparative effectiveness research
CJRR	California Joint Replacement Registry
CPT	Current procedural terminology
CRN	Coordinated Registry Network
CRT	Cardiac resynchronization therapy
DES	Drug-eluting stent
EC	Ethics Committee
EHR	Electronic health records
FDA	Food and Drug Administration

GCP	Good clinical practices
GHTF	Global Harmonization Task Force
GUDID	Global UDI Database
GWU	George Washington University
HBD	Harmonization By Doing
HITECH	Health Information Technology for Economic and Clinical Health
HIVE	High Performance Integrated Virtual Environment
ICD	International classification of disease
ICOR	International Consortium of Orthopedic Registries
IDE	Investigational Device Evaluation
IFU	Instruction for use
IMDRF	International Medical Device Regulators Forum
IOM	Institute of Medicine
IP	Intellectual property
IRB	Institutional Review Board
IVCF	Inferior Vena Cava Filters
MAT	Manual Aspiration Thrombectomy
MDR	Medical device reporting
MDRTF	Medical Device Registry Task Force
MEDCAC	Medicare Evidence Development & Coverage Advisory Committee
MIS	Minimally invasive surgery
NCD	National Coverage Decision
NCDR	National Cardiovascular Data Registry
NIH	National Institutes of Health
OPC	Objective performance criteria

PAS	Post-approval study
PHI	Protected health information
POP	Pelvic organ prolapse
PPP	Public-Private Partnership
PRO	Patient reported outcomes
PRR	Proportional reporting ratios
PSO	Patient safety organization
PVD	Peripheral vascular disease
PVI	Peripheral vascular interventions
RCT	Randomized controlled trials
RRT	Randomized registry trial
SAE	Serious adverse events
STEMI	ST-elevation myocardial infarction
STS	Society of Thoracic Surgeons
SVS	Society of Vascular Surgery
TAVI	Transcatheter aortic valve implants
TJRR	Total Joint Replacement registry
TPLC	Total Product Life Cycle
TVT	Trans-catheter Valve Therapies
UADE	Unanticipated adverse device effects
UDI	Unique device identification
VA	Veterans Health Administration
VQI	Vascular Quality Initiative

Introduction:
Synopses of Chapters Comprising the MDRTF Report

Brief Background of the Task Force

In September 2012, the U.S. FDA released "Strengthening Our National System for Medical Device Postmarket Surveillance," a report providing an overview of FDA's medical device postmarket authority and the current U.S. medical device postmarket surveillance system. In 2014, a multi-stakeholder Planning Board was created and funded to identify the governance policies, priorities, and business models necessary to develop a sustainable national system for medical device postmarket surveillance. At the same time, a call was issued for volunteer experts from a broad range of stakeholders to contribute to a national Medical Device Registries Task Force (MDRTF). The Task Force was mandated to consider both the objectives and the logistics of leveraging existing and evolving electronic registries, records, and even mobile technologies in the structure of such a national system. At the launch meeting in Washington, DC on June 24, 2014, FDA leadership further articulated the intention of the national system to reach beyond simply fulfilling regulatory needs. To that extent the Task Force, from its very first meeting, reshaped the objectives of its recommendations for the National System in two fundamental ways: 1) from a dedicated postmarket surveillance system to a National Medical Device Evaluation System poised to address optimal pre- and postmarket balance by impacting the TPLC through continuous benefit/risk & safety data accrual; and 2) from a dedicated regulatory decision support system to a national health resource capable of providing customized, informative data, and thereby a truly unique value, to all stakeholders in the medical device ecosystem. Operationally it was recognized that these recommendations fundamentally encourage a National System poised to erase the traditional, artificial and redundant separation of clinical care data from clinical research data, while addressing currently unmet needs of both. This report summarizes the deliberations of the Task Force.

Planning Board Recommended Implementation Approaches and Priorities

Years 1-2: Initiate an incubator project tasked to develop a 5-year implementation plan for MDS through fact finding activities and pilot programs. The Board recommends that the incubator project should be initiated by FDA, adequately staffed and resourced, and guided by a multi-stakeholder group with relevant medical device experience.

Years 3-7: The second phase of work will focus on the MDS implementation plan produced by the incubator project. Once selected, the MDS PPP's leadership should set and oversee the system's strategic development priorities, begin to build and sustain broader stakeholder participation, oversee implementation of the organizational plan, and establish system performance measures. Some of the important challenges the MDS PPP must address during implementation include:

—Supporting a multi-pronged approach to ensure widespread adoption and use of UDIs in electronic health care data

—Minimizing the burden of data capture and sharing

—Developing policies to ensure the protection of patients and their privacy

—Building the capabilities to provide value to a broad group of stakeholders

On February 23, 2015, the Planning Board publicly shared its recommendations for a "*National Medical Device Postmarket Surveillance System"…which "supports optimal patient care by leveraging the experiences of patients to inform decisions about medical device safety, effectiveness, and quality in order to promote the public health*." In conjunction with this thorough and thoughtful report, a 7-year implementation plan was outlined (see inset). To avoid confusion or diffusion of effort, the Task Force recommendations have been constituted as a conceptual framework that is flexible and scalable, enabling implementation within the scope of those recommendations.

Framing the Dialogue

Strengthening the postmarket device environment has two obvious features that the Task Force recognized as central to launching FDA's interests in a national system for medical devices: 1) safety is the most important but challenging aspect of device behavior and 2) the full range of stakeholders in the medical device ecosystem is most visible in the postmarket—many physicians and patients are only aware of or exposed to devices after they have been approved for use in the national commercial marketplace.

However, the Task Force also recognized that to improve both the quality and efficiency of medical device evaluation fundamentally requires eliminating gaps in and fragmentation of device-related data, and that in contemporary devices landscape one of the largest gaps is in the segmentation of research efforts that separate premarket from postmarket studies. This construct strongly supports the 2014-2015 CDRH priorities to approach the "balance" between pre- and postmarket evidence, not as two independent entities but as a continuum. And this continuum was also recognized as eventuating from the original CDRH construct of the TPLC, which was formulated not as a series of disarticulated steps but as a model of the continuous accrual of benefit/risk and safety knowledge about devices related to a disease-specific therapy.

The Task Force thus elected to refer to the objective of these recommendations not as a surveillance system, but as a National Medical Device Evaluation System. Strengthening the postmarket system itself provides an important example of the impact of such a shift. As safety signal detection has improved—which clearly has been the case over the past decade—it has also produced newspaper headlines, public angst and criticism of device evaluation processes, including criticism of FDA—that have significantly slowed innovation. With the National Device Evaluation System envisioned by the Task Force, detection of a safety signal in the postmarket could organically both add efficiency and better inform the ability for manufacturers to use such signals as engineering targets and to convincingly demonstrate signal mitigation with newer, better device designs that reach the public faster—in other words, it could both stimulate and facilitate innovation. By eliminating gaps in data accrual and applying standardized definitions over the TPLC, the National System can transform the most challenging areas of device evaluation, stimulating medical industry while building widespread confidence, interest and public trust that the National System is designed to protect and promote the public health through facilitated, ongoing medical device innovation.

The Task Force proposes a path forward that combines advances in infrastructure interoperability, quality, and data access with progressive development and implementation of structured core minimum data sets and standardized data dictionaries. This path moves medical device information from the current state of idiosyncratic heterogeneity that may generate false signals or obscure real signals to the more informative actual heterogeneity of specific devices, operators, patients, regions, and outcomes that inform device benefit/risk and safety considerations. Methodologically, this moves statistical considerations and study designs from managing heterogeneity as a source of potential misinformation to a National System that aggregates true heterogeneity into assignable domains with an enriched ability to integrate the real dimensionality of clinical practice data into research-grade outcomes analytics. Along this path, the Task Force literally recommends enriched dimensionality of devices, device procedures, patients, operators and device outcomes as a bridge better linking clinical practice and research questions of device benefit/risk and safety.

Ongoing registries and EHRs provide critical infrastructure fundamental to the timely implementation of such a National System. Many existing registries are already self-sustaining and fully operational, and well-positioned to leverage "dual purpose" activity in support of a National Medical Device Evaluation System on a fairly immediate basis, greatly minimizing the cost or development resources needed. However, the Task Force recognized that no single existing entity contains all the elements necessary to provide robust, ongoing device evaluation, such as unique device identifiers, operator proficiency, technical procedural information, long term follow up, or large enough patient cohorts. Furthermore, specific disease states and device classes vary greatly—from what kinds of clinical outcomes are most essential to capture, to some device areas where mature registries and data structure do not exist. Adopting a wider view of existing resources, the Task Force recognized that in many instances the deficiencies of any single registry or data source could be corrected if it was linked to one or more additional registries, strategically selected to produce a complementary network whose whole data composite in fact could support ongoing and robust device evaluation. This structure has been termed the "strategically coordinated registries network," or CRN—even with the recognition that many key elements in such networks; e.g., EHRs, administrative claims data or mobile device outputs, may not actually be registries per se.

To promote and propel this construct, the Task Force strongly embraced the execution of proof-of-concept pilot projects. Criteria for prioritizing such projects are recommended, including: their ability to yield both immediate impact on specific device areas and concomitantly to deliver generalizable predicates and tools applicable to other device areas; the breadth of stakeholder engagement in the project; and the leveraging of existing national resources and standards.

Successful examples of such data linkages already exist, such as the Transcatheter Valve Therapies (TVT) registry linked to administrative claims data to combine robust device- and procedure-related data to long term follow up for indication extensions, and the International Consortium of Orthopedic Registries' (ICOR) use of a global distributed network for safety signal

detection. However, these efforts are themselves highly segmented from one another, and the systems interoperability solutions that they represent have not been catalogued for reuse in other areas. Thus to both provide relatively immediate momentum as well as create the long term, the Task Force also recommends that CRN-based partnerships, interoperability solutions, standardized definitions and other such tools should be actively catalogued in the public domain to encourage their reuse across CRNs, creating an organic substrate growing the long term foundation of the National System, and that an active and defined entity within the National System be developed for this task.

The Task Force recommends the CRN approach leveraging reusable tools at the systems level because it encourages both the maximum implementation of standardized informatics and structured data and an ongoing flexibility to adapt to changes in infrastructure and information technology over time. Where today device and other registry networks constitute the most visible and established opportunity for dual-purpose leverage, over time EHR development may provide a more seamless platform from source documentation. Patient reported data through mobile technologies and objective data collected outside of traditional healthcare facilities also represent fast moving technologies with increasing interest for research applications. The National System will need to be able to adapt without being completely reinvented, and the CRN structure provides such adaptability without compromising the foundational stability or quality of the device data accrual per se.

The Task Force further recognized that existing, operational registries and health record systems also have existing governance structures, providing another source of systems-based variability and complexity for integration into a CRN. It is obvious that if such entities perceived CRN governance or participation as a loss of independence, or "dual purposing" as added work and added cost, there would be powerful disincentives to creating the networks. On the other hand, if tangible incentives resulting from inclusiveness in CRN governance structure or from the augmentation of existing registries in concert with other participating entities were actively identified and emphasized, CRN participation could clearly represent a truly exciting range of novel opportunities to serve both their original missions and the public health concomitantly. For instance, if enhanced, standardized device data accrual produced better benefit/risk and safety information, inclusively governed CRNs would be in an excellent position to convey updated information to specific stakeholders customized to their interests as patients using the device, doctors implanting the device, regulators making decisions about the device, manufacturers innovating the device, or payers understanding device cost relative to other therapies. Along similar lines, the Task Force also noted the degree to which variability in current stakeholder participation across existing registries, when integrated into a CRN, constitutes a novel and enriched array of avenues for expanded stakeholder involvement, from very local or device specific roles in a particular CRN to opportunities for involvement in the National Medical Device Evaluation System as a whole. This level of deliverables is considered by the Task Force to carry and convey sufficient value in both spirit and substance to overcome

what otherwise could constitute an unmanageable spectrum of barriers and complexity in developing the National System.

Finally, in framing the dialogue, the Task Force felt strongly that the key to successful strategically coordinated registry networks, to integrated governance of existing entities and to perception of opportunity across stakeholders--the key to both the success and the sustainability of the National System--would fundamentally depend on the ability of some defined and active entity within the National System to actively develop a medical device ecosystem culture of goodwill and trust supporting precompetitive collaboration and partnering. While a responsible approach to cost considerations and funding is mandatory, the Task Force felt clearly that money alone would be insufficient to generate, much less to sustain or to grow, a National Medical Device Evaluation System.

Existing Medical Device Registry Models and Leverageable Efforts

Even in device categories with the most mature existing registries, the development of appropriately focused and configured CRNs to address device-related benefit/risk and safety constitutes a substantial effort. Assessment of existing medical device registry models provides both information about where leverageable efforts and resources exist, as well as a range of potential lessons learned in how they are configured. For example, some registries require dedicated data entry independent of clinical workflow, while others illustrate means of extracting device-related data from EHRs, eliminating both the added work and potential errors intrinsic to data reentry. Existing examples thus illustrate the need to convert processes for systematic collection of high quality clinical data from a clinical trials information model to an informatics model of data management and extraction. In this context, the Task Force recommends ubiquitous adoption of both unique device identification (UDI) and patient identification from point of manufacture through end of patient life, and adoption into the health information systems of healthcare enterprises, from point of entry in the supply chain through billing. In conjunction with CRNs and the National System, conjoined UDI and unique patient identification, whether via direct identifiers or via approaches that preserve privacy, promote analytic options that can both allow for accurate patient matching and resolve issues of informed consent. This approach supports and associates critical device follow-up and the association of patient outcomes. It also facilitates CRN integration of registries and EHRs that provide consistent capture of clinical outcomes over sufficient duration to meaningfully inform a longitudinal perspective.

Ideal Characteristics of a Coordinated Registry Network (CRN)

The function and quality of information that can be provided by a strategically integrated CRN will be limited primarily by the presence of any participating entity with limitations that cannot be rectified by integration with other complementary registries, EHRs, or data sources. Thus, the Task Force recommends that registries, EHRs and other sources participating in CRNs should be well characterized as stand-alone entities, as well as by the presence of open architecture elements that could facilitate their integration into the CRN without excessive re-design.

The Task Force recommends five fundamental principles to guide priorities in creating integrated CRN functionality. These principles include:

1) The ability to identify medical devices;
2) The use of standardized clinical vocabularies, common data elements, and outcome definitions;
3) Plans for selecting and creation of generalizable interoperability solutions for linking disparate data sources;
4) Plans for creating partnered, inclusive governance; and
5) Plans for developing value-based incentivized sustainability.

Functionality of CRN structure and governance should be guided with the objective of meeting the needs of multiple stakeholders including patients, clinicians, healthcare systems, FDA, registry owners, and industry partners. Functionally, leveraging and linking of participating registries and other entities should promote ongoing device evaluation, increase patient and device data and outcome information quality, modulate added work load through dual-purposing existing workflow, and so reduce cost and enhance overall efficiencies and timelines associated with regulatory milestones. Impact on such milestones should include the entire TPLC, from early feasibility and premarket pivotal approval studies to postmarket safety signal detection and proof of safety signal mitigation by innovative device iterations.

Priority Medical Device Opportunities

The flexible and scalable nature of the CRN structure in developing the National Medical Device Evaluation System supports customization across medical devices, both in the data and outcomes that warrant collection and in the variability in existing registries and related infrastructure elements from one device area to another. A pragmatic approach to organic growth of the National System should include some principles for prioritization of device opportunities where successful CRN development and functionality will provide momentum for similar developments in other device areas.

Recognizing the need for early, illustrative successes, the Task Force recommends that device priorities include both opportunistic and conceptual elements. Opportunistically, device areas where good will, partnered governance, linked registries, and functional benefit/risk and safety analytics already exist should be prioritized with regard to advancing CRN models and identifying systems features and lessons learned to facilitate similar programs in other device areas.

Conceptually, the Task Force recognizes existing work that has categorized ten medical device characteristics that warrant prioritization for improved, registry-based evaluative systems, and that fit well with the needs of an evolving National Medical System. Specifically, these characteristics include:

1) The consequences of device failure are serious for the public health, leading to serious disability or death;
2) Rapid uptake of the device is expected and adverse events are likely to be rare but very serious;
3) The device uses new technology whose long-term safety and effectiveness are not well understood;
4) The device type has substantial design variations;
5) Performance of the device may vary significantly across the population or across sex or racial subgroups;
6) The procedure outcome is highly dependent on operator performance;
7) Costs related to application of the device are substantially higher than current therapy;
8) More specific information is needed to establish best practices for the device;
9) Unanticipated problems with similar devices have been identified; and
10) The devices require significant patient interaction to collect patient-centered outcomes.

Examples of contemporary devices that could be profiled for such prioritizations include: hip replacement devices, knee replacement devices, spine surgery procedures/devices, vascular procedures/devices (peripheral, abdominal aortic aneurysm [AAA] repair, carotid and vascular access/catheters), cardiac valves, atrial fibrillation ablation procedures/devices, implantable rhythm and heart failure devices, coronary stents, robotic and other minimally invasive surgery devices, ophthalmic procedures/devices, and surgical mesh.

Identification and Optimization of Analytical Methodologies for Device Evaluation

CRN structure for device evaluation will inevitably involve heterogeneity in data collection, patient populations, clinical centers and operators. Information aggregated to the component registry level (e.g., distributed summaries) may be sufficient for some medical device performance activities, such as signal detection, but may be insufficient for other activities, such as benefit/risk determinations. Key aspects of CRN construction include attention to minimizing idiosyncratic heterogeneity affecting data quality (variability in data definitions, missing data, measurement error, etc.) that intrinsically undermines the interpretability of analytic results. On the other hand, the linked infrastructure and implementation of structured data sets and standardized definitions supporting poolability promote an enriched capacity to capture true heterogeneity of device, operator, patient, hospitals and outcomes and assign them to appropriate domains. This shift from idiosyncratic to actual heterogeneity in medical device data sets greatly advances the opportunity to analyze device performance and outcomes on the basis of the true dimensionality of clinical practice with more robust, research grade interpretability.

For signal detection, leveraging the CRN architecture requires consistent, standardized data that sufficiently specify the medical devices under study and that contain the outcomes of interest. Bodies of data with consistent quality, standardized definitions, and device identification from registries in a CRN structure can also serve to summarize information vital for premarket study designs, in addition to capturing the efficiency opportunities of prospective registry-based randomized trials. Thus CRN based statistical methodologies and models positively impact device evaluation throughout the TPLC.

Perception, Ethical and Related Considerations: Keys to CRN Sustainability

The flexibility of operational CRN structure implies a challenge to decision making processes that will determine what architecture is best suited to specific device applications. Both perception of and actual inclusiveness in governance surrounding such decisions is likely to affect the necessary partnering across existing registry or resource owners, and hence the success of the CRN itself. For instance the dynamic to compile a CRN for distributed or hybrid systems across registries within a common therapeutic area will be quite different from CRN a central data architecture model that extracts a single device-related core minimum data set from multiple broader data sources such as EHRs. The Task Force recommends that successful models of inclusive governance leading to productive CRNs, and lessons learned from unsuccessful attempts to develop CRNs, should be centrally collected and catalogued for public domain access for reuse in new CRN efforts and growth of the National System.

Participation of patients both in the CRN architecture and with regard to access and use of their private health data related to medical devices is also a critical feature of CRN development. Implicit in bridging the gap between clinical care and clinical research is the need for a thorough re-examination of the definition of research as well as the ethical formulations of informed consent and privacy permissions. Patient engagement in the development of best practice approaches to these issues will predictably be related to patient willingness to allow access to their personal information in support of device evaluation and overall CRN functionality. The Task Force encourages CRNs to support or develop software applications and other means for patients to directly contribute to and to control their health data and concomitantly facilitate the consent process, dissemination of research findings and notification of device users of new safety concerns, alerts, or recalls. As a key example of customizing deliverables to stakeholders, the Task Force recommends that CRNs prioritize information management and contextualization strategies customized to device patients. This recommendation should be aligned with the broader priority for CRNs to both determine immediate strategies of how to best leverage and customize existing mechanisms of medical device benefit/risk and safety to better meet specific stakeholder needs, as well as to determine longer term strategies promoting more novel means to aligning information dissemination with specific stakeholder needs.

Summary

The National Medical Device Registries Task Force strongly supports the construct of a National Medical Device Evaluation System that endeavors to eliminate gaps in evidence generation over

the entire TPLC and concomitantly, eliminating the redundancy and artificial contemporary separation between clinical care and clinical research data. The Task Force recommendations propose a path forward that shifts data capture across multiple sources from difficult-to-interpret, idiosyncratic heterogeneity to an enriched substrate reflecting the dimensionality of device use, procedures, and outcomes to inform both clinical and research interests. Such a National System should be tasked to deliver priority benefit/risk and safety information customized to specific stakeholders, while preserving in its mission and priorities the support of better, faster approaches to regulatory decisions.

To accomplish this end, leveraging existing electronic registries clearly provides the most robust path forward both in opportunities for ongoing, informative data capture and, through dual purposing and partnering, with a minimum of time to productivity, added work beyond existing workflow, new systems development and cost. Compensation for the intrinsic insufficiencies of any single registry or other data source is accomplished through strategically integrated CRNs that develop partnered governance and reusable interoperability solutions across complementary data sources. The CRN structure also supports both the ability of the National System to be flexible and resilient to changes in electronic health information while supporting an ability to identify and catalogue partnering and interoperability solutions for reuse in different device areas, promoting foundational stability of the National System overall.

The success and sustainability of CRNs, and of the National System itself, will depend on the actively promoted transformation of the contemporary medical device innovation ecosystem from a landscape of fragmentation, skepticism, and distrust to a culture of good will and partnering in every aspect of the CRN and National System's development and operations. CRNs and the National System will require responsible financial support, but their sustainability will depend on the overall ability to provide processes, engagement and deliverables of such value that stakeholders will share the perception of the System as a truly priceless healthcare resource.

Historical Background

In September of 2012, the FDA released a report entitled "Strengthening Our National System for Medical Device Postmarket Surveillance," which provides an overview of FDA's medical device postmarket authority and the current U.S. medical device postmarket surveillance system proposing four specific initiatives, intended to strengthen the medical device postmarket surveillance system in the United States using existing resources and under current authorities.[1]

An update to the report, issued in April 2013, details the concrete steps that the Agency will complete to develop an integrated system that efficiently and effectively achieves its four basic functions, from timely identification of postmarket signals to facilitating premarket device clearance and approval.[2]

On June 24, 2014 in Washington, DC, the MDRTF was convened to consider both the objectives and the logistics of leveraging existing and evolving electronic registries and related tools toward the production of a national medical device evaluative system. The purpose of this system is explicitly mandated to reach beyond regulatory science and address potential deliverables across the range of stakeholders invested in medical device innovation – patients, physicians, hospitals, payers, manufacturers, regulators and other federal professionals. The Task Force was thus designed to include experts from that broad range of stakeholders in the medical device ecosystem. Furthermore, the purpose of this system is clearly envisioned to address not only postmarket surveillance but to influence the TPLC, in alignment with the 2014-2015 CDRH priorities to enhance pre- and postmarket balance and to optimize clinical trial designs supporting regulatory decisions). This report summarizes the deliberations of the Task Force.

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Chapter I. Framing the Dialogue on a National Medical Device Evaluation System

Roles for and Lessons from Device Registries

In a world of rapidly proliferating digital information and communication systems, interest in and the potential utility of electronic information for health care purposes has never had broader or deeper advocacy. For medical device innovation in particular, electronic information combined with state-of-the-art analytic methodologies holds promise for a major shift in the device evaluation landscape, more efficiently and robustly connecting benefit/risk assessment, residual safety concerns and safety signal detection in an integrated system that accrues information continuously throughout the TPLC of the device and its competitive iterations. As summarized in Table 1, high-quality electronic information sources strategically integrated as CRNs have the potential to 1) provide more robust benefit/risk assessment for regulatory decisions; 2) enhance the speed and accuracy of safety signal detection, confirmation and escalation, as well as documentation of safety signal mitigation resulting from corrective actions or the emergence of safer device designs; 3) provide profound operational efficiencies including lowering costs, accelerating clinical trial enrollment and shortening timelines from design to bedside; 4) enhance transparency and dissemination of device data oriented to specific stakeholder groups (regulatory decisions, reimbursement decisions, best practice guidelines, manufacturing targets for device innovation, patient information and education); 5) promote operational elements critical to analytic methodologies (such as implementation of UDI, structured minimum core data sets and standardized outcome definition dictionaries enhancing data poolability; 6) promote re-usable interoperability solutions across existing systems rather than requiring development of de novo systems for every device or for the National System per se; 7) promote international regulatory convergence, further eliminating redundancies and time delays leading to excessive cost and regional device lag for innovative new device development programs. Integrating strategically complementary registries, EHR and other electronic data source as device specific, customized CRNs thus promotes standardized data definitions and systems solutions with concomitant flexibility in the system infrastructure, even as new modalities of electronic health information and patient-centered tools continue to evolve. The CRN approach is intended to provide scalable steps and reusable systems and partnerships as the foundational architecture of the National System, promoting a learning medical device health system applicable to both clinical care and clinical research needs.

While referred to throughout this report as a “registry” network, the scope of electronic healthcare infrastructure intended as candidates for participation in the CRNs includes many electronic data repositories that might not otherwise be classified as a “registry” per se; e.g., EHRs, administrative claims data, and patient-centered smart phone or mobile applications, to mention just a few. The MDRTF envisions a National System of CRNs whose central structure includes one or more participating registries, as classically defined by the Agency for Healthcare Research and Quality (AHRQ):

> *"An organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.[1]"*

Another definition of "registry" that serves this purpose is the one offered by the multi-stakeholder Registry Working Group of the International Medical Device Regulators Forum:

> *"An organized system with a primary aim to improve the quality of care that uses observational study methods to collect relevant data and evaluate outcomes relevant to patients, and, comprehensively covers the population defined by exposure to particular device(s) at a reasonable generalizable scale (national, regional or health system)."[2]*

CRNs will likely need to include other non-registry electronic data repositories, and (especially with the advance of standardized EHRs) if better options become available, the CRN structure is not actually intended to be defined by the "registry" component as such.

In summary, integrating contemporary electronic information infrastructure as strategically CRNs for health care purposes provides the conceptual and pragmatic basis for an unprecedented National Medical Device Evaluation System that both engages and uniquely provides value to each of the stakeholders who make up the medical device innovation ecosystem.[3,4] Such a system could not only advance postmarket constructs such as a national medical device surveillance system,[5] but bridge medical device clinical practice information needs, clinical research information needs and ongoing accrual of medical device information as a learning evaluative capability throughout the TPLC.

Table 1. Objectives of CRNs Leveraged toward a TPLC National Medical Device Evaluation System

Objective	Impact
1. More robust benefit/risk evaluation	a. premarket pivotal approval decisions b. postmarket labeling extension decisions c. pre-/postmarket balance
2. More robust safety evaluation	a. residual safety concerns pre-/post-approval b. safety signal detection c. safety signal escalation d. more efficient demonstration of safety signal mitigation with newer devices
3. More efficient device evaluation pathways	a. lower clinical trials costs leveraging dual purpose registry infrastructure b. faster trial enrollment with lower site-based burden using routine clinical workflow pathways c. shorter design to bedside timelines for better, safer devices
4. More transparent, stakeholder-oriented dissemination of device-related data	a. inform regulatory decisions b. inform reimbursement decisions c. inform best practice guidelines d. inform manufacturing targets for device innovation e. inform patients
5. Promote operational elements supporting analytic methodologies	a. implement UDI b. implement standardized, structured minimum core data sets and outcome definitions c. enhance data poolability across heterogeneous data sources
6. Promote interoperability solutions	a. defer need to develop completely de novo health data systems b. confer flexibility to CRNs and National System overall
7. Promote international harmonization of device reporting and evaluation	a. advance regulatory convergence efforts b. enhance device availability across international markets c. support international safety surveillance modalities d. implement standardized minimum data sets and outcomes definitions in native languages
8. Create a flexible "learning" electronic infrastructure capable of supporting a learning health care system	a. leverage existing electronic registries, health records and other relevant data repositories b. integrate new electronic resources as they become available c. integrate novel patient-centered information tools as they become available
9. Promote novel avenues of stakeholder engagement	a. integrate local, regional, national advisory and governance opportunities b. prioritize stakeholder-oriented access and deliverables

In the face of this vision, the actual diversity of systems, system developers, and stakeholders, as well as perceptions of unmet needs and pace of change in all of these areas constitutes a substantial catalogue of challenges. To date many registries containing medical device procedural and outcomes data, as well as other electronic data repositories with medical device-related information, have been developed for individual hospitals, hospital systems and health care payers; for manufacturers using clinical trial case report forms and databases; for regional

and national systems; for state authorities, federal agencies and professional societies around the world. Even as each of these systems may represent the state-of-the-art for its purpose, no one system exists that is sufficient for medical device evaluation. Furthermore, in their siloed and heterogeneous formats there is currently little ability to synthesize information or continuously accrue safety or benefit/risk knowledge. On the other hand, recognizing and leveraging the level of excellence, commitment, resources and success invested across this legacy of efforts, a national agenda to systematically and collaboratively integrate complementary and informative data across these efforts seems far more likely to promote public health better and faster than could any attempt to simply replace them all with any single centralized system. For instance, not only are many device registries already fully functional for their intended purpose, but in many hospitals they have already been incorporated into site-based clinical workflow. Thus dual purposing existing registries through strategic integration into CRNs could efficiently leverage the available data without taxing site-based staff and physicians with additional workload.

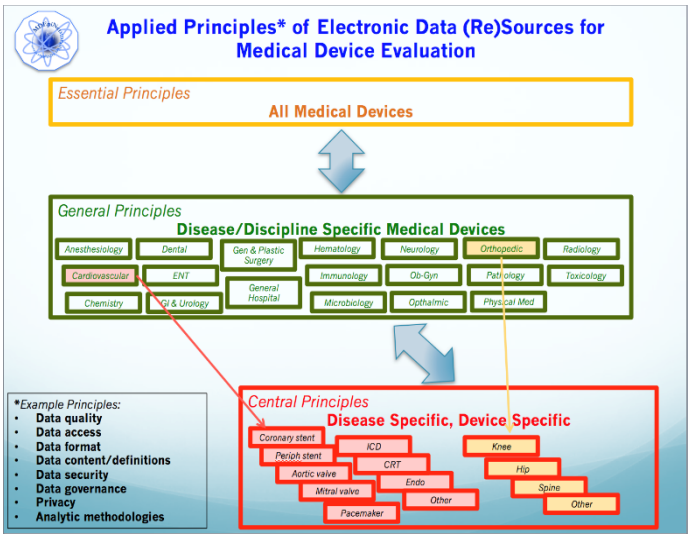

Figure 1. Applied principles of electronic data (re)sources for medical device evaluation.

Furthermore, the diversity of medical devices, their composition and performance metrics, their manufacturers, the concerns of patients who use them and the skills needed by physicians who deploy them must also be accommodated if the concept of a national evaluation capability is to progress beyond a philosophical premise. Thus, the construct of the National System must balance the efficiency of common *essential principles* for all device evaluation (e.g., good quality data, complete data, standardized definitions, etc.) with the more divisive need for more granularity in actual applications. As illustrated in Figure 1, essential principles of device evaluation using electronic data must be distilled into more granular *general principles* related to therapeutic areas such as cardiovascular, orthopedic, ophthalmologic or gynecologic practice and devices. And even within specific therapeutic disciplines, for impactful regulatory science applications such general principles must be further detailed into device-specific *central principles* related to a coronary stent, or heart valve, or defibrillator or prosthetic hip or knee if a National Medical Device Evaluation System is to achieve practical functionality.

In developing recommendations for such a National System the Task Force recognized the prohibitive complexity of defining a “one size fits all” system at this point and time. To provide recommendations, however, that could both support a long term vision of a National System and identify immediate scalable steps that could provide momentum and foundational elements

for the future, a series of nine principles for the report were developed as the thematic core of the recommendations, with more detailed exploration of key issues subsequently. The core principles constitute this chapter, with more detailed explorations in chapters 2-6.

Principle 1: Informing the Total Product Life Cycle (TPLC) of a Medical Device

Pragmatic Pre- and Postmarket Focus for the National Medical Device Evaluation System

The TPLC is a conceptual framework for looking at any product or its competitive iterations from cradle to grave; it represents the market-driven evolution of a device from initial concept through development to widespread market use and finally to obsolescence and replacement by subsequent generations of products or new transformative technologies. Intrinsic to the TPLC concept is an iterative device design and learning process driven by the continuous accrual of safety and benefit/risk mechanistic and clinical information. As shown in Figure 2, such learning may occur during the developmental stages of a single device or, as the competitive marketplace brings forward new designs, through the comparative performance of older vs newer generations as the device pipeline evolves.

Ideally, as the device pipeline matures, the required evidence and other barriers for further regulatory decisions decreases--the study for the first generation of a breakthrough technology like a coronary stent may be a randomized superiority design, while for a 10th generation stent the required human investigational exposure and clinical trial resources may be significantly less. Practically, processes delivering enhanced efficiency and enhanced quality to support regulatory decisions currently face many barriers and challenges. Many of these barriers are not regulatory issues per se—for instance the reluctance of clinical sites to add research work load to currently busy clinical work flow, and the reluctance of patients to participate in clinical research they may perceive as a departure from clinical care—are barriers throughout the TPLC.

Sustainable CRN infrastructure can positively impact research and development timelines and cost throughout this entire pre- and postmarket spectrum. Positive engagement of patients as stakeholders, leveraging clinical work flow through dual purpose data element ascertainment, and integration of standardized data dictionaries including descriptor and outcomes well support any relevant study designs—including prospective randomized registry-based trials that have been shown to ease site workload/workflow burden shorten enrollment timelines and reduce study costs.[6]

Applied to early feasibility and pivotal randomized studies of breakthrough technologies, premarket timelines from prototype to market could be shortened. Sustained CRN use of standardized data elements, data capture processes and data dictionaries over an entire device pipeline could dramatically facilitate regulatory decisions for indication extensions for approved devices and for approval of newer iterations of approved devices. A contemporary example is the use of ACC/STS TVT registry data linked to administrative claims data,[7] (see text box). Longitudinal CRN infrastructure implementing standardized data elements methodologically enhances the poolability of data, and thus the accrual of knowledge. In a maturing device pipeline, such infrastructure would also accrue much larger patient cohorts, as well as longer-term follow-up information. A large cohort of patients with long-term follow-up and standardized outcomes would support a more robust ability to define objective performance criteria and performance goals, to inform Bayesian priors or to otherwise robustly move to less expensive and less time consuming clinical trials for later stages or iterations of the device.

The TVT Registry serves as the data collection tool for an FDA continued access protocol (CAP) for the Edwards Sapien 3 heart valve. This allows continued enrollment of patients in a protocol after a clinical trial has been completed and while the marketing application is being reviewed by FDA. Use of the TVT Registry facilitates this CAP by obviating the need for the manufacturer to develop a registry specifically for the study. This will greatly simplify the data collection process and dramatically reduce the administrative burden for this CAP. Reduced requirements regarding source document verification has been approved by FDA. Industry will carry out on-site monitoring; post-30 day follow-up will be managed by the current TVT Registry process. Medicare claims data linked to TVT Registry data will be used for patient follow up 1-5 years post-procedure. This demonstrates the use of an existing device registry in the premarket space.

To provide not only efficiencies but also better inform device evaluation, CRN structures linking currently available registry and other electronic data resources will need to carefully assess the selection and definition of data elements, and ensure that common data dictionaries are used across linked resources. Such assessment and alignment of standardized data definitions used across linked resources will encourage the adoption of such definitions throughout registries, EHRs and other components of the national health care infrastructure. Progressive adoption of standardized definitions, enhancing poolability of data elements, further enhances methodologic capability to meaningfully pool device identifier and outcomes data across clinical and observational trials devices, better informing benefit/risk and safety information accrual related to such devices.

Another key element for vigilance in the development of CRNs is validation of event ascertainment. Outcome events reported by registries, by clinical trials and by administrative claims data, for instance, may vary in the degree of source data monitoring needed to confirm reporting accuracy, adjudicate by specific criteria, or identify oversights. Even EHRs, which constitute “source data” for most clinical trials, have inconsistencies and omissions that must be determined and managed in the evolution of both CRNs and a National Medical Device

Evaluation System that progressively leverages registry and EHR data over time. Once validated, CRN structures are well positioned to convey both efficiency and enhanced poolability and data quality for device evaluations ranging from premarket early feasibility and pivotal studies to automation of postmarket signal detection.

Leveraging CRN infrastructure over the TPLC also provides a particularly powerful tool for ameliorating residual safety concerns, replacing fragmented approaches to data collection with more consistent data structure and content, and thus with more reliably poolable data sets that support accrual of knowledge. Poolability of outcomes across clinical trials and even across specific generations of devices is greatly enhanced when standardized outcome definitions have been implemented. Such poolability is most critical to early and accurate detection of rare but catastrophic safety events such as stent thrombosis. In longitudinal registries, using identical data structure and endpoint definitions, the ability to subsequently demonstrate mitigation of the safety signal by targeted device design engineering may be greatly facilitated.

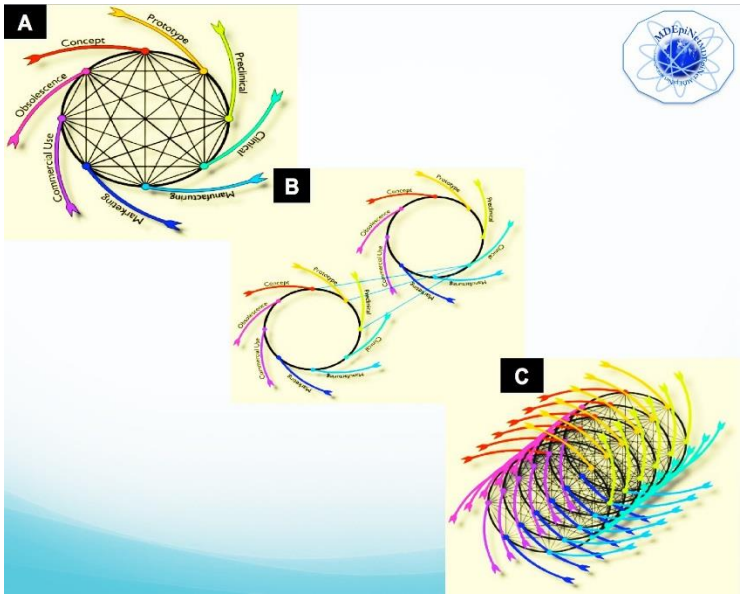

Figure 2. The TPLC information accrual concept for A) a single device, B) progression from one device design to another and C) through the maturation of a device pipeline. (Courtesy of David Feigal, MD)

When enhanced safety signal detection is conjoined to proof-of-signal mitigation by newer device models using CRN infrastructure, safety signals shift from generating media headlines to providing engineering targets for manufacturers building new, safer devices. Such a system can concomitantly promote public and scientific confidence in the safety of new technology and in medical device evaluation processes in general, as well as informed flexibility around the pre- vs. postmarket balance, and will support better devices coming to the bedside faster.

Principle 2. Linking "Complementary" Registries and Data (Re)sources to Overcome Single-Source Deficiencies: The Strategically Coordinated Registry Network (CRN) Solution

Many data sources, such as electronic health records (EHRs) or some existing registries, do not contain all the elements necessary to document the full dimensionality of device evaluation. However, linking registries and other complementary external data sources through interoperability solutions could produce a network whose data composite supports ongoing, robust device evaluation. The MDRTF recommends a National Medical Device Evaluation System

constructed through the progressive integration of existing registries (device registries or disease-based registries) with one another or with non-registry electronic data sources (EHRs, administrative claims data, etc.) that contain complementary information; e.g., where information available in each data source corrects key deficiencies of the other. These enriched, integrated complementary electronic source data configurations are termed CRNs.

The composition of electronic data suitable for device evaluation across disparate but complementary registries or other data sources necessitates a variety of interoperability solutions. Executed in a specific device application, it is highly likely that these solutions can provide programmed tools to facilitate similar applications for other devices. Through this and similarly shared lessons learned, the CRN construct promotes a scalable and organic approach to "growing" a National System over time, while being both quickly productive and extremely flexible in how to best configure a CRN across a broad range of medical device and stakeholder needs.

Some examples of interoperability approaches currently being applied in conjunction with device registries are shown in Figure 3. For instance, if one registry was rich with information about the device and the deployment procedure but had little follow-up information, and another registry had long-term follow-up but little information about the device and procedure, linking the two complementary registries at the level of patients common to both would yield a much richer resource than would either registry alone. This model has been used successfully in the Transcatheter Valve Therapies registry linkage to administrative claims data. In another approach, if much larger cohorts or regional information on a particular device outcome was sought that was not available at any single registry, identification of a minimum core data set whose data elements use standardized definitions combined with and the development of a portfolio of structured data capture tools could efficiently pull core data sets from multiple registries, multiple EHR systems and other sources to be compiled into a single patient-level data set (see Project Proposal below). A third model, particularly applicable to safety surveillance, would be outcomes distilled from even more independent sources in a distributed data network model. This model has been used very successfully in postmarket orthopedic implants by the ICOR.[8]

The quality of CRN-based data will be only as robust as its weakest participating component. Thus, criteria for registries or relevant data sources participating in CRNs should be developed, and should emphasize standardized international coding conventions (UDIs, international classification of disease [ICD] codes, current procedural terminology [CPT] codes and data dictionaries, Healthcare Common Procedure Coding System [HCPCS], etc.), completeness and accuracy of data, etc.

Finally, the progressively accelerated pace of both medical device innovation and IT platforms and electronic health information sources requires a flexible, adaptable infrastructure. Registries as we know them today may very well cease to exist in the foreseeable future, as EHRs, patient reported data, claims data and social media progressively evolve for both clinical

and clinical research purposes. With that in mind, the Task Force recommends advancing the National System through device-specific CRN structures as the means to provide both enrichment of available device information and flexibility in structure to accommodate contemporary times.

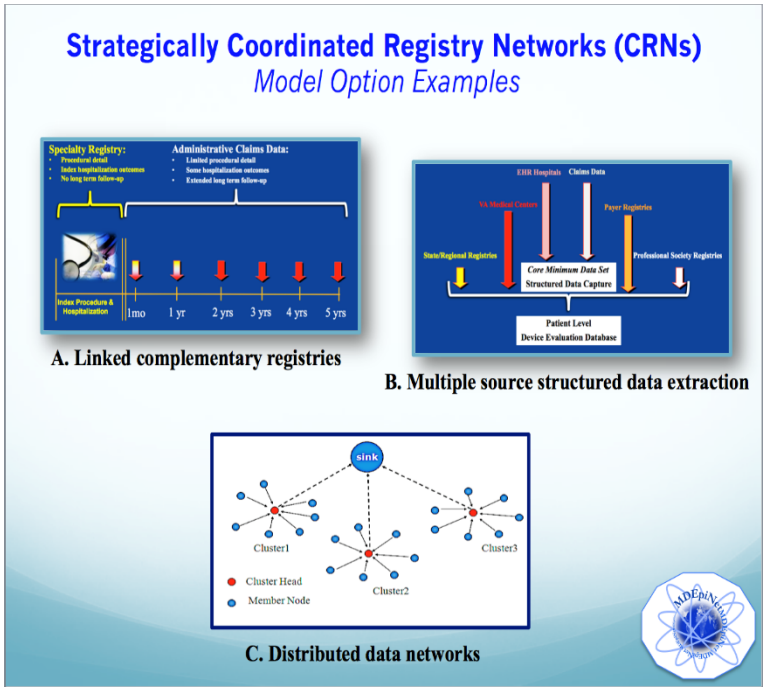

Figure 3. Examples of interoperability constructs for CRNs (Modified, courtesy of Matthew Brennan, MD)

The CRN construct thus provides the fundamental capability to leverage and still overcome limitations of incomplete, siloed data sources while being adaptable to specific device and stakeholder needs and resilient over time without being committed to any particular programming, registry or data source. Successful partnering and interoperability solutions from CRNs in any one device area are likely to provide important efficiencies when applied through CRNs in other device areas, creating both near term enhancement of device-related benefit/risk data accrual and long term, organic growth of an internally consistent National Medical Device Evaluation System.

Principle 3. Work with the Present, Look to the Future

While the vision of a world unified by electronic health information that promotes a learning health system has never been clearer or more widely shared, its execution for medical device evaluation remains profoundly complex. Almost all of the topics considered in this report look very different depending on whether the discussion concerns the best use of existing resources or the best vision using resources that are currently under development or that should be developed in the future. The Task Force considers both perspectives critical, as immediate advances will help the National System gain momentum, while longer term development will progress toward more comprehensive objectives. Thus this report is intended to present constructs of integrated near-term (present) and longer-term (future) recommendations. Also in this spirit, the Task Force recognizes that near-term solutions will promote making things better but not perfect, and that the road to the big changes all stakeholders advocate, through the complexities of the current environment, will best be travelled through small, successful steps.

Flexibility, adaptability and resilience of the strategic CRNs over time are thus seen as central to the successful development of near term enhancement to evaluation in selected medical device

areas while progressively growing focused CRN structures into new device areas, facilitated through lessons learned and reusable tools developed in the earlier phases, such as interoperability solutions and incorporation of structured, standardized data elements.

Similarly, the use of key pilot projects (see below) to create transparency, tangible deliverables and an enhanced sense of progress and return on investment is also considered critical to successfully reshaping the device evaluation landscape along the lines of the proposed National Medical Device Evaluation System.

Principle 4. Build on Existing Concepts and Effort

In executing its mission, the Task Force sought to create recommendations to move things forward, not go over established ground. Thus documents already conveying substantial thought on registries as infrastructure for medical device evaluation, including publications and statements from AHRQ,[1] AdvaMed,[9] Pew Charitable Trusts,[10] the NHLBI,[6] and the Planning Board,[11] are referenced rather than re-stated wherever possible.

Similarly, the MDRTF structurally emphasizes, especially for early phase development of the National System, linking of existing resources to create composite capabilities beyond those of any single source, and without the cost and delays of building an entirely new resource from the ground up. Operationally and methodologically this supports the notion of augmenting benefit/risk and safety data by integrating complementary data sources. Beyond operations per se, this approach is critical to the development of partnering opportunities central to the composition of CRNs. For instance, if existing registries with operational infrastructures perceive the National System as potentially imposing a mandate to assume new governance oversight, or add work, complexity or cost in the course of "dual purposing" they will be unlikely to consider partnering in a CRN. On the other hand, the degree to which a CRN and National System convey recognition of the accomplishments and the unique value of existing registries, with participation in CRNs constituting an incentivized opportunity for growth and enhancement by building on those accomplishments, the opportunity for partnering is most likely to meet all stakeholder's objectives.

Principle 5. Envisioning the National Medical Device Evaluation System as an Ecosystem Construct Rather Than an FDA Construct

The shift within the Center for Devices & Radiologic Health at FDA from a historically reactive agency chartered to protect the public health to a more proactive agency promoting the public health has been evidenced by multiple innovation-oriented CDRH initiatives. These include launching the MDRTF, with instructions to consider a National Medical Device Evaluation System that would serve all stakeholders, not simply the FDA. In fact, the Task Force considered a strong sense of the National System's value across stakeholders to be a key element to its sustainability. While incorporating a broad range of perspectives and objectives, the Task Force also recognized that regulatory constructs and guidance documents, such as the TPLC, benefit/risk assessment, patient-reported outcomes and safety surveillance, provide useful frameworks around which to design a National System. Thus while the Task Force considered it

critical that the National System accommodate and provide value for stakeholders in addition to FDA, it also considered a central role for regulatory constructs appropriate and even critical to formulating the focus of recommendations for the National Medical Device Evaluation System. This Task Force report therefore is intentionally aligned with FDA strategic priorities, including the 2014-2015 CDRH Strategic Priorities,[12] the Postmarket Strategic Plan[13] and Update[14] and the five focus areas detailed in the Medical Device Epidemiology Network (MDEpiNet) MDRTF Call for Nominations.[15]

Principle 6. Creating and Sustaining a Culture of Collaboration and Trust

The Task Force recognizes that the success of even the most accessible and immediate steps forward leveraging existing, complementary data resources will require unprecedented good will and pre-competitive, collaborative partnering across particular stakeholders, across professional specialties, across federal agencies and across competitive manufacturers. The Task Force thus also recommends a priority focus on developing an active and sustainable mechanism to foster a culture of good will. Mechanisms such as transparent PPPs that can foster ongoing dialogue and trust and a pragmatic focus along these lines will be a fundamental component of a sustainable National Medical Device Evaluation System. This entity cannot simply be an assumption—it will require an organized, dedicated resource within the National Medical Device Evaluation System.

In this spirit, this report is intended both as an instrument through which to consider the structure, purpose and evolution of a National Medical Device Evaluation System, and as an instrument through which to open avenues of engagement throughout the medical device ecosystem itself. While the Task Force writing group was limited in size, its reach to colleagues and peers via MDEpiNet PPP committees, centers, programs and operations was incorporated in this report's focus on specific scenarios, directions and pilot projects. This report is not envisioned as a final blueprint but rather as a door opening to invite new views and voices into the dialogue launching the vision and approaching the implementation challenges and solutions for the National Device System.

Principle 7. Achieve Sustainability through Perception and Partnership

Insights into the operational costs of any registry-based system are often considered the defining principles for developing sustainability strategies. For the national medical device system, the Task Force considered managing expenses as necessary but not sufficient to achieve sustainability. While there are many important details and variations as to how revenues and cost savings could actually be distributed to particular stakeholders with implementation of a national device evaluation system, there is also clear consensus that safer, better medical devices reaching the bedside more quickly support robust economic models in both public and private sectors. Thus sustainability of a national medical device evaluative system that eliminates redundancy, enhances the quality of information (especially with regard to safety concerns), removes barriers and time delays for regulatory milestone decisions and increases stakeholder involvement and transparency in the process and the data is not simply a financial

model. The perception of such a system as trustworthy, confidence in how it is governed and the sense of opportunity for participation and partnering among stakeholders in its mission, governance, operations and deliverables all foster the sense of the critical value of the system itself.

Furthermore, the emphasis on value reflective of broad stakeholder participation works essentially with the flexibility imparted by the CRN structure to optimize the opportunity for balanced and comprehensive analytics promoting a truly learning health system in the medical devices sector. The ability to re-titrate risk models over time depends on sustainable, longitudinal, standardized data. Similarly, once a safety signal is detected, the ability to efficiently show subsequent mitigation of that safety signal as newer, better device designs emerge depends on sustainable CRN activities. The ability to shift safety concerns from media-driven headlines to balanced and scientifically grounded public information, and to shift the detection and confirmation of safety signals from sources of panic to discrete targets for engineering innovation—including the ability to mitigate such signals with design enhancements—is far different from the conservative and relatively distrustful environment of today. In this light, the Task Force considered the most critical element of the medical device evaluative system's sustainability going forward to depend on its being seen as a national health care "treasure," wherein its sustainability is one of its most informative and precious features.

The structure of the CRN itself brings together participating entities, each and all of which contribute some novel elements to the overall ability of the CRN to provide efficient and informative device evaluation. By virtue of this very structure, a broad range of novel avenues for local, national, professional or other stakeholder involvement and engagement is opened. In an atmosphere of good will, collaboration and trust, such an enriched range of opportunities for involvement is envisioned as another key feature of the ongoing ability of the National system to establish and sustain a living dialogue supporting a learning medical device evaluation capability.

Principle 8. Pilot Projects Promoting a Catalogue of Generalizable Tools, Partnerships & Principles for a National System

CRNs as part of the National Medical Device Evaluation System are intended to integrate the operation of currently disparate but complementary systems including such areas as interoperability processes for sharing information, development of shared analytical methodologies and, at a basic level, to impact how organizations and people interact to achieve system goals in an actively developed culture of collaboration. Such tools and partnerships are considered the means for enhancements offered to all stakeholders by the evolution of a National Medical Device Evaluation system, both in the quality of benefit/risk and safety information and in the overall efficiency of workflow and cost across clinical care and clinical research activities.

Panel 1. Essential Characteristics of Pilot Projects

Answers immediate, discrete disease-specific/device specific research question
Demonstrates & operationalizes generalizable predicate applicable to other device evaluation applications ("use, re-use, recycle" emphasis)
Leverages existing national infrastructure efforts & resources

Applies recognized national standards for data structure & definitions

Reduces duplication, complexity & redundancy (promotes efficiencies)

Includes & empowers multiple stakeholders

The MDRTF recognizes that innovative systems development tools and partnerships cannot simply be mobilized conceptually, but must be both mobilized and demonstrated through discrete pilot projects. The Task Force recommends that projects should be prioritized with regard to defined, essential characteristics related to the development of CRNs and, through the CRNs, to the organic growth of the National System itself. Essential pilot characteristics should include the delivery of immediate results related to well-articulated device-related research questions, illustration and implementation of novel partnerships and systems integration and interoperability processes that can be generalized to applications beyond the immediate device under study, leveraging of existing national infrastructure (EHRs, professional and payer registries, administrative data, etc.) and standards and data dictionary efforts (such as CMS, ONC, and FDA and standards development organizations such as HL7 and ANSI X12), support for methodologies that reduce duplication and complexity (e.g. of trial design, device identification and other key data capture, data quality, event ascertainment, event adjudication), and encourage inclusion and empowerment of relevant stakeholders. These characteristics are summarized in Panel 1.

Even as the Task Force embraces pilot projects as critical to the evolution of the National System, and supports the Planning Board[11] observation that without aggressive funding of a broad and diverse portfolio of pilot projects, the present and future of the National System will progress slowly. However, the MDRTF also recognizes that launching a broad portfolio of diverse pilots with some central coordination and cataloguing risks producing a counterproductive diffusion of effort and expertise. In fact, a broad portfolio of diverse, standalone pilot projects risks producing a fragmented range of work products that could actually promote redundancy and contentiousness across advocates of multiple solutions to the same applications.

Thus, to ensure that an enriched portfolio of pilot projects actually promotes the capabilities, the focus and the organic growth of the National Medical Device Evaluation System across the CRNs, the MDRTF strongly recommends the provision for an entity dedicated to the identification of generalizable deliverables (partnerships, interoperability tools, core minimum data sets, data element dictionaries and other work products amenable to re-use in multiple areas of device applications or by multiple CRNs) and to their cataloguing and readiness for public access, use and re-use.

As with so many of the Task Force recommendations, the ability to successfully implement such an entity across CRNs and across pilot projects will require execution in an active atmosphere of good will and partnering. If project leaders or participants primarily perceive the coordinating entity as imposing a loss of independent governance, an added work load or added expenses, no federal mission or funding per se will achieve the growth of a well standardized, efficient, high quality device evaluation capability for the National System.

The MDRTF approach to pilots complements the recommendations of the Planning Board,[11] to create core system capabilities through a 1-2 year incubator project. Specifically, the Task Force pilot projects are consistent with the Planning Board recommendations to: demonstrate value for individual stakeholder groups, prioritize opportunities to leverage existing resources, ensure patient protections and data privacy requirements, and identify and prioritize initial pilot projects to inform the implementation of the National Medical Device Evaluation System infrastructure.

Principle 9. Creating a Global Community of National Jurisdictions

As medical therapies have successfully mitigated infectious disease in most of the developed world, chronic and acquired disorders associated with aging, such as heart disease, cancer, lung disease, musculoskeletal, gastrointestinal and genitourinary dysfunction, have become the dominant unmet needs in health care. Concomitantly, the use of medical devices and concerns regarding their benefit/risk, safety, surveillance and cost have rapidly become a global agenda. Currently, experience with human subjects for many devices begins outside the United States, meaning more complete integration of such experience would advance the maturity of the TPLC at all stages. Furthermore, most large device manufacturers already provide devices to markets globally. In this sense the Task Force recognizes that an ecosystem approach to medical device evaluation should necessitate an international perspective, even while acknowledging that accommodating differences in international jurisdictions and cultures, as well as languages, will add new challenges to the complex array of issues to be resolved.

Many principles fundamental to the evolution of a National Medical Device Evaluation System apply to the broader ecosystem view that extends device benefit/risk evaluation from American public health interests to the global community. The Task Force's emphasis on developing means such as the PPP to encourage pre-competitive collaboration in developing CRNs for a national system is similar to the need for fostering good will in the international setting to advance regulatory convergence as the gateway for all medical devices to the bedside. Examples of previous such efforts include the Global Harmonization Task Force (GHTF), Japan-USA Harmonization By Doing (HBD) and, more recently, the International Medical Device Regulators Forum (IMDRF).

As recommended by the Task Force, infrastructure solutions that are both flexible and strategically linked have the potential to provide common data quality, standardized definitions and multiple other features that could enhance regulatory decision making and therefore regulatory convergence. Such infrastructure paired with robust benefit/risk analytic

methodologies could not only put regulators on equal footing for milestone decisions and safety signal detection/confirmation/mitigation, but also substantially eliminate needs for redundant expensive, time-consuming clinical trials and even reduce the risk to human subjects participating in such trials. In a scientific sense, the extension from national to international medical device evaluative systems along the lines of this Task Force's recommendations could position stakeholders globally to literally be able to speak the same benefit/risk language.

Chapter Summary Points

1. Existing registries/electronic data repositories all have deficiencies for medical device evaluation. Flexible strategies for linking and /or extracting data across interoperable registries and non-registry whose data complement one another can correct such deficiencies. Applied to specific device areas, such entities can be developed as strategically Coordinated Registry Networks (CRNs).
2. CRN structure can enhance both the quality and efficiency of device evaluation from early feasibility and pivotal approval trials to postmarket detection and mitigation of safety signals by new, better device designs. The CRN based National System thus can most robustly support stakeholder clinical and research needs for medical devices throughout the TPLC.
3. While regulatory frameworks are useful for implementing a medical device evaluation system and for systematically addressing the TPLC, benefit/risk and safety surveillance, the fundamental construct of one system serving many stakeholders must be prioritized.
4. Sustainability of data flow using standardized definitions enhancing poolability through CRNs enable ongoing accrual of knowledge, informing a learning health system capable of re-calibration of risk models, more efficient proof of safety signal mitigation over time as new device designs emerge, and more efficient clinical trial designs that better leverage historical comparators and encourage registry-based prospective randomized trials.
5. While sustainability of the medical device evaluation system includes cost considerations, the usefulness will be defined by stakeholder-specific deliverables that have "value beyond cost."
6. A dedicated entity for cultivating a culture of pre-competitive collaboration, good will and trust, such as public-private partnerships, is essential to promote the success and sustainability of a national device evaluation system.
7. Pilot projects concomitantly delivering disease-/device-specific advances and predicates generalizable to other devices will best promote small pragmatic steps advancing toward an optimal National Device Evaluation System. A dedicated entity to ensure that generalizable elements (partnering, interoperability solutions, structured data sets and data dictionaries) are identified and catalogued in the public domain to encourage use and re-use across projects is essential to ensure that projects advance, rather than diffuse, the evolutionary process of the National System itself.
8. International focus encouraging regulatory convergence and the more efficient accrual of knowledge about device benefit/risk across multiple global markets should be an important part of a medical device "ecosystem" approach to device evaluation.

Pilot Projects

Project I.

Combined Diagnostic & Therapeutic Investigational Device Evaluation (IDE) coronary devices

- Prospective, randomized registry-based IDE study for labeling extensions of approved diagnostic and therapeutic devices
- Linked procedural registry and administrative claims data infrastructure
- Public health data informing optimal care in seniors suffering MI
- IDE Study: Optimal revascularization strategy in elderly suffering ST-elevation myocardial infarction (STEMI)

1. Disease/device focus	a. coronary artery disease (STEMI) b. coronary drug-eluting stent (DES) platform IDE c. diagnostic coronary instantaneous flow reserve (iFR) wire IDE d. radial vs. femoral access in elderly suffering STEMI
2. Immediate research question(s)	a. clinical outcomes with iFR guided complete revascularization vs. infarct artery only standard care (randomized) b. clinical outcomes with single DES platform for STEMI (performance goal) c. bleeding complication reduction & health care economics in elderly using radial access (historical comparator)
3. Stakeholders engaged	a. patients: optimal care for seniors with CAD b. regulators: two imbedded prospective data-driven IDE decisions for labeling c. NIH/NIA: public health information in seniors with CAD d. industry: partnered effort across two manufacturers (DES and iFR devices) e. payers: impact of bleeding reduction, improved outcomes in seniors with STEMI f. professional societies: leveraging registry base; inform best practice guidelines
4. Existing national resources leveraged	a. ACC-NCDR Cath-PCI registry (acute procedural data) b. CMS administrative claims data (long term follow up) c. MDEpiNet PASSION Programs d. CDISC/ONC standardized definitions
5. Efficiencies promoted	a. reduced site-based workload (auto-population of database elements directly from registry sources) b. shortened trial duration (enhanced site interest & enrollment rates) c. reduced study costs (partnered industry sponsors with shared trial costs; reduced case report form development and site training)
6. Applied national standards & definitions	a. ARC & ICD-9/10 data element definitions implemented across registry infrastructure b. CDISC and Global UDI Database (GUDID) data elements and data dictionaries c. ACC structured data

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Chapter II. Existing Medical Device Registry Models and Leverageable Efforts

In a dynamic healthcare environment characterized by 1) the rapid introduction of breakthrough technologies necessitating robust tracking and monitoring, 2) the expansion of value-based healthcare requiring systematic improvements in processes and performance and 3) a new-found focus on patient-centeredness creating the opportunity to capture the patient's voice, the need for reliable, valid data has never been greater. Device registries have emerged as one solution for capturing, aggregating and quantifying the benefits and risks of devices, including short-term and long-term outcomes. Medical device registries typically include detailed data about patient exposure to devices, information about those devices, detailed information about pathology, co-morbidities and clinical outcomes. Exposure may correspond to use of a diagnostic device such as magnetic resonance imaging or implantation of a device such as a specific type of artificial hip. Because the device operator, whether a surgeon, non-surgeon interventionist or technician, can impact device performance, medical device registries also include operator identifiers that can identify characteristics predictive of operator-dependent effects. Finally, information regarding patients' concomitant therapies is usually captured to characterize device-therapeutic interactions that may occur.

Given the systematic collection of these key data, existing registry infrastructure could support device surveillance and benefit/risk evaluation. Features of existing registries provide lessons learned and strategic leveraging potential as participating components of CRNs for both near- and long-term functionality of a National System. This chapter describes registries that have supported meaningful postmarket device assessments, highlighting several examples across the field, and assesses their degree of readiness for expansion to the needs of a National System composed of CRNs that addresses the TPLC.

Current Device Registry Landscape

Across the United States, there are hundreds of ongoing registries at the local, state and national levels, many of which capture medical device data. Other stand-alone, FDA-mandated postmarket condition of approval registries are often conducted by manufacturers. Even more registries are developed and housed within public and private integrated health delivery systems. While these initiatives vary in terms of purpose, methods of data capture and analytical strategies, modest incremental reconfiguration could leverage many of them to contribute to a National Medical Device Evaluation System. Many ongoing and sustainable registries offer elements of infrastructure that are well positioned to contribute to a National System, not only in content but through their implementation into daily work flow in participating hospitals. On the other hand, single purpose registries, such as condition-of-approval single-arm studies, may answer selected device evaluation questions but do not lend themselves to the needs of a National System. The presence of a National Medical Device Evaluation System may eliminate the need for and costs related to such single-purpose studies altogether.

Professional Society-Based Registries

Many professional societies (e.g., the American College of Cardiology [ACC], the Society of Thoracic Surgeons [STS], the American Heart Association [AHA], the Society of Vascular Surgery [SVS] and the American Academy of Orthopedic Surgery [AAOS]) have developed national or regional registries that collect clinical, device and procedure-specific data, with most focusing on a procedure as the index event, often with only short-term follow-up.

The ACC National Cardiovascular Data Registry (NCDR) portfolio,[1-3] in collaboration with sister professional societies, collects extensive data about cardiac catheterization and percutaneous coronary interventions (CathPCI Registry), implantable cardioverter-defibrillator procedures (ICD Registry), congenital heart disease catheterization procedures (IMPACT registry), carotid artery and peripheral vascular interventions (PVI registry), acute myocardial infarction (ACTION-GWTG registry), transcatheter aortic valve replacement implants (STS/ACC TVT Registry) and ambulatory care (PINNACLE). The CathPCI Registry, augmented by data from a subset of voluntary hospital participants, was used to confirm medical device reporting (MDR) concerns that the VasoSeal closure device was associated with a significantly higher risk of adverse outcomes after angiography than other such devices.[4,5] This and other similar NCDR-related applications[6] in postmarket surveillance help illustrate the potential for ongoing professional society registries to enhance postmarket device evaluation.

The STS-ACC TVT Registry was launched in December 2011. The TVT registry captures clinical data on transcatheter aortic valve procedures conducted in non-federal hospitals. The registry was created to comply with Centers for Medicare & Medicaid Services (CMS) coverage and payment criteria for Medicare patients undergoing commercial transcatheter valve procedures. This mechanism encourages all patients undergoing TAVR to be enrolled in the registry. The registry was expanded to include mitral valve procedures in 2014. The TVT Registry 1) is a joint venture between the ACC and the STS; 2) includes a broad stakeholder steering committee including regulatory and payer representation from both FDA and CMS; and 3) includes an advisory group consisting of the above stakeholders along with representation from patient advocates, consumer groups, AHRQ, industry representatives and other professional societies. As of March 2015, there were 365 hospitals participating with over 32,000 unique patient records (not including non-commercial implants). The TVT registry has several additional unique aspects, including: 1) accrual of patient quality-of-life data at baseline, 30 days and 1-year post implant; mortality at discharge and 30 days; 1-year follow-up reports for both TAVR and mitral leaflet clip procedures (extended to TMVR in 2015); 2) a robust Web-based physician event adjudication process assessing peri-procedural complications including TIA, stroke and re-interventions; and 3) formal site audits. The TVT registry has been utilized by FDA and industry as infrastructure for IDE studies (e.g., TAVR alternative access), post-approval studies and continued access programs (e.g., Edwards Sapien 3 intermediate risk).

While illustrative of enhanced postmarket signal confirmation, the lack of long-term follow-up and small number of sites in the VasoSeal example would be insufficient for many other device benefit/risk evaluations. A current example of one approach to benefit/risk evaluation through a device registry is the STS-ACC TVT registry.[7,8]

Comparing and contrasting these two registry-based examples identifies several practical issues, including the importance of 1) enhancing the timeliness and quality of data collection and reporting, 2) accruing longitudinal follow-up of clinical outcomes, 3) integrating site-based data entry strategies with clinical workflows to reduce the burden of data collection, and 4) potentially leveraging EHR systems in the future for all of the above. Finally, it is also clear that the needs to provide postmarket surveillance, e.g. safety signal detection and confirmation, are different from those to evaluate device benefit/risk.

Government-Based Registries

The United States Veterans Health Administration (VA) Clinical Assessment Reporting and Tracking (CART) Program[9,10] is a national clinical quality program for VA cardiac catheterization laboratories. It uses a clinical software application and is a primary example of integration with the (VA) EHR. The CART software enables standardized clinical data entry at the point of care using data elements and definitions from the ACC's NCDR. The software is implemented as part of routine clinical documentation workflow in the EHR.[11]

The CART Program was specifically designed to support medical device surveillance. Used by all VA cardiac catheterization laboratories, the CART system software includes data fields to capture any "unexpected problems with medical devices used during the procedure."[12] The data capture fields are purposefully broad to allow the description of all problems with any medical equipment used during a cardiac catheterization procedure. The medical device fields are automatically flagged in real time following data entry and are collated from all VA catheterization labs for review by the CART Coordinating Center. The medical device reports are assigned priority levels in order to identify those with the highest probability of safety issues related to design or manufacturing. Under a 2008 Memorandum of Understanding, the VA CART Program regularly shares the information it captures about potential problems with medical devices with the FDA, and is a clinical partner of the FDA MedSun Medical Product Safety Network.

CART Program: In an analysis of 260,258 consecutive cardiac catheterization or percutaneous coronary intervention procedures between 2006 and 2012, Tsai et al. reported 974 unexpected medical device problems from 76 VA cardiac catheterization labs.[12] Of those, 235 (24%) were identified as possibly or likely related to a medical device defect. In Fiscal Year 2014, VA cardiac catheterization labs performed 12,248 PCIs and recorded 265 medical device reports (2%). The majority of reports of unexpected problems with medical devices was ultimately not device-specific issues but rather related to patient risk or procedural details such as a failure to deploy a device due to heavily calcified blood vessels.

While the CART Program is in many ways a model for active device surveillance, there are potential limitations to its broader implementation. First, the scope of CART is confined to cardiac catheterization and PCI procedures. Second, integration of CART requires agreement, commitment and education of clinicians at all sites. Third, the VA has a single EHR that enforces standardized data capture but is not used outside the VA system. Fourth, the VA system provides resources for 1) CART Coordinating Center personnel to manage the CART system, 2) the processing of device-related adverse event reports, and 3) clinician time for review of the reports and interaction with FDA. Fifth, CART lacks UDIs or other device identifying information such as lot numbers. Finally, while CART is highly leveraged for VA and FDA needs, it has not evolved to accommodate other stakeholder needs.

The VA CART Program demonstrates the feasibility of an active medical device surveillance program. It combines structured data capture with standardized national clinical registry data elements. It leverages the EHR for point-of-care capture of potential device issues. It evaluates all reports of potential medical device issues and routinely shares this information with FDA. The addition of longitudinal data analyses, expansion to a broader number of medical procedures and real-time location tracking technology to capture all medical device implant information are ongoing initiatives anticipated to further enhance the CART device surveillance program.

State-Based Registries

The Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2)[13] is composed of two statewide quality improvement projects: (1) a prospective multicenter statewide registry of consecutive percutaneous coronary interventions (BMC2 PCI); and (2) a prospective, longitudinal multicenter statewide registry of consecutive peripheral vascular disease (PVD) interventions, vascular operations and carotid interventions (BMC2 VIC). Participation in these programs is voluntary. Both projects collect, audit, analyze, and report procedural variables and outcomes to individual operators and institutions. Data collection uses standardized data elements and definitions harmonized to support participation in the ACC NCDR registries. BMC2 collects additional detailed cardiovascular procedural information beyond that captured in the NCDR, including additional detail about medical devices along with the use of new drugs.

BMC2 can potentially support medical device evaluation given the device data being collected, detailed clinical phenotyping information and access to longitudinal outcomes. The PCI registry collects data on all patients undergoing PCI in participating hospitals while BMC2 VIC enrolls the majority of patients undergoing vascular surgery and PVD procedures. Data collection is facilitated with financial support from the registry sponsor for a dedicated study coordinator who ensures timely submission of data. The coordinating center regularly trains study coordinators to ensure data quality and consistency, and all sites are audited. Furthermore, the coordinating center provides analytic resources.

Medical Device Safety Findings from BMC2:
(1) Risk of Acute Kidney Injury after Percutaneous Coronary Interventions Using Radial Versus Femoral Vascular Access: Insights From the Blue Cross Blue Shield of Michigan Cardiovascular Consortium.[14]
(2) Comparative Safety of Vascular Closure Devices and Manual Closure among Patients Having Percutaneous Coronary Intervention.[15]
(3) Impact of Automated Contrast Injector Systems on Contrast Use and Contrast Associated Complications in Patients Undergoing Percutaneous Coronary Interventions.[16]
(4) Percutaneous Coronary Intervention Complications and Guide Catheter Size: Bigger is Not Better.[17]
(5) Manual Aspiration Thrombectomy (MAT) Does Not Impact Short or Long Term Survival in Primary PCI: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Collaborative (BMC2).[18]

To date, BMC2 has not been used as a medical device evaluation platform. However, a number of findings have been published from BMC2 that suggest it could be leveraged for device evaluations. These include evaluations of procedural complications and longitudinal outcomes, comparative safety of medical devices, associations between medical device use and procedure complications and associations between medical device use and longitudinal outcomes.

Finally, state-mandated registries exist for a number of procedures that feature the use of medical devices, including coronary artery bypass graft surgery and PCI. Mandatory reporting of PCI outcomes has been in place in New York since 1991, Pennsylvania since 2001, Massachusetts since 2003, with New Jersey mandating the collection of data (without public reporting) since 2007. The focus of these registries has been on improving health care quality through public reporting. As with BMC2, these registries all have the potential to be leveraged for device evaluation applications and have already produced a number of ad hoc device analyses. State-based registries thus have much promise to contributing to the National Medical Device Evaluation System as participating components of CRNs.

Health Care Organization-Based Registries

The Kaiser Permanente integrated health care system supports the National Total Joint Replacement Registry (TJRR).[19] TJRR is a national payer-based database designed for the clinical evaluation of elective total hip and knee replacement; it currently includes information on over 1.5 million implants. The TJRR provides mechanisms for 1) monitoring of revision, failure and

rates of key joint device complications (e.g., infection, venous thromboembolic disease such as blood clots and embolism and mortality), 2) stratifying patients at risk of poor clinical outcomes following total joint arthroplasty, 3) identifying the most effective techniques and implant devices (best practices and implant constructs), 4) tracking implant usage and costs and 5) monitoring and supporting implant recalls and advisories in cooperation with FDA.[20] The Kaiser Permanente integrated health care model is ideally suited to harness the power of the TJRR as it is tightly coupled with broader clinical source data. Standardized documentation of pre-operative, operative, and follow-up clinical data combined with patient characteristics, surgical techniques, implant characteristics and longitudinal clinical outcomes is linked with device-specific information as long as the patient remains enrolled with the payer system. The information is used to track device failures and to optimize best practices for device implementation. Data flows to the Kaiser Permanente implant registries database from multiple information portals across the Kaiser Permanente Health Connect Suite, including inpatient and outpatient sources covering admission, discharge and transfer data, health information management, patient clinical records, pharmacy, emergency department, operating room and billing. Data from ancillary services including outpatient pharmacy, laboratory, radiology/imaging, EKG, immunizations and transcription services also flow into the registry. TJRR illustrates integration between a device registry and one payer's EHR portals, permitting efficient feedback to clinicians and patients in terms of device recalls and advisories.

Kaiser Permanente National Total Joint Replacement Registry has been instrumental in evaluating longitudinal outcomes, implant comparative effectiveness, patient- and device-specific risk-factor identification predicting device failure, surgical site infection surveillance and medical center- and physician-specific variations. Data modeling has resulted in the creation of revision risk calculators. Active feedback and communication with clinicians led to documented evidence-based practice changes (e.g., less use of smaller femoral head sizes led to longer device survival). Kaiser Permanente is instituting automated postmarket surveillance for adverse event detection along with national and international collaborations leveraging existing registries, electronic health records and large administrative databases. [21-24]

The TJRR is thus well-positioned to inform a National Medical Device Evaluation System as a participating CRN entity. The systematic accrual of standardized data across healthcare delivery serves as a mature construct for the larger model of universal device surveillance and benefit/risk evaluation. Limitations of this model include the governance of data by a single private entity and the lack of complete data in patients who receive care both within and outside the Kaiser system, or who leave the Kaiser system.

Patient Safety Organization-Based Registries

A patient safety organization (PSO) is a group or institution formed to improve medical care by reducing medical errors. The structure of a PSO offers several opportunities for creating device registries or enhancing a national medical device system. The Patient Safety and Quality

Improvement Act authorized the creation of PSOs in 2009 to improve the quality and safety of health care by collecting and analyzing patient data.[25]

> *"Organizations that are eligible to become PSOs include public or private entities, profit or not-for-profit entities, provider entities such as hospital chains, and other entities that establish special components to serve as PSOs. By providing both privilege and confidentiality, PSOs create a secure environment where clinicians and health care organizations can collect, aggregate and analyze data, thereby improving quality by identifying and reducing the risks and hazards associated with patient care."* [26]

PSO members can submit patient-identified data for safety and quality improvement work within a PSO without the need for informed consent or Institutional Review Board (IRB) approval, but cannot identify patients, providers or hospitals in any publication. Such identifiers allow matching with external databases, such as the Social Security Death Index or Medicare claims data to identify late outcome events from independent sources.

PSOs can be developed through many mechanisms. In one mature example, the SVS developed a PSO for its Vascular Quality Initiative (VQI) in 2011.[27] The VQI is a multi-specialty consortium organized to improve the quality, safety, effectiveness, and cost of vascular health care. The consortium uses a unique distributed network of regional quality groups to analyze and improve practice.[28] Granular clinical data are collected at the time of device implantation as well as one-year follow-up data from providers' offices. The VQI ensures submission of all procedures by annual audit against hospital or physician claims data.

The Society for Vascular Surgery's Vascular Quality Initiative Patient Safety Organization provides non-identifiable data (by patient, hospital and provider) on an individual procedure basis to industry and FDA for postmarket surveillance projects. Aggregate data reports are generated, and data monitoring or adjudication is performed by an independent steering committee within the PSO. Core lab imaging data, if desired, can be submitted to the PSO and linked with the patient data to be included in the project. Because all procedures of a given type are entered by each center, including those using the new device being evaluated, it is possible to develop a simultaneous comparison with all other similar device types to build a contemporary control group. The VQI uses a Vascular Technology Committee to maintain an infrastructure for such projects and the required communication with industry and FDA. Evaluation of medical devices used for vascular healthcare has become an important quality focus of the Society for Vascular Surgery's PSO.[27,28]

VQI is currently being used to collect data for two medical device post-approval surveillance studies in collaboration with industry and FDA. All 340 VQI participating centers are invited to participate, which provides more of a real-world perspective than typical industry-sponsored studies. Sites can be reimbursed through the PSO for additional data or follow-up reporting, which increases efficiency by eliminating the cost of individual site contracting by industry. Further efficiency is gained because patient consent and IRB approval

are not required to collect patient-identified data. These identifiers allow matching with the Social Security Death Index file or claims data to supplement late survival or end-point calculations. Specific device details are collected including the manufacturer's product number or device name and size in sufficient detail to cross-reference to a product number. Because most patients receiving vascular devices are Medicare beneficiaries, PSO data has been matched with Medicare claims to measure re-interventions or other key outcome events. By using a single vendor web-based system for data entry, the VQI can readily add dynamic content to its existing registries for new device evaluation projects. The vendor contracts with physicians to report data as a Qualified Clinical Data Registry to meet CMS Physician Quality Reporting System reporting requirements, enhancing value and thus potential for sustainability of the registry effort.

The PSO approach thus resolves a key dimension: the matching of patients across data sources. The safe haven created by the PSO legislation successfully addresses one key barrier to longitudinal outcomes assessment. Another characteristic is the capture of the universe of the specific devices that are the subject of the PSO. However, similar to other types of registries, limitations include portability and scalability to a more generic and universal device surveillance ecosystem, along with the constraints against expansion imposed by the PSO statutes. Already including professional societies, manufacturers, hospitals and patients, the PSO approach has clear potential to engage and enhance regulatory and related federal stakeholders and contribute to a national medical device evaluative system.

International Consortia

CRNs leveraging current registries and linking information across data assets that reside outside of the registries face challenges integrating disparate data sources. These issues may be particularly relevant for international device safety surveillance and/or benefit/risk evaluations. One successful example is the ICOR,[29] which has convened representatives from the international community around specific points of interest such as metal-on-metal hip implants and fixed-bearing versus mobile-bearing knee replacement implants. In these evaluations, the role of ICOR has been to identify discrepancies among registries, address heterogeneity in definitions and develop advanced methodologies to generate knowledge that can be generalized among countries. In fact, the ICOR collaboration has compellingly argued that outcomes-based rather than biomechanics-based evidence should guide development and adoption of new orthopedic devices.[30] Even these limited successes serve as pilot examples of how an approach of sharing harmonized data can clearly permit more precise quantitation of effects and outcomes. While still evolving as a network and in its infrastructure, ICOR is a novel example of the critical role of good will and collaboration toward addressing common device safety concerns. Both locally and internationally, this kind of good will and collaborative effort across stakeholders will be an essential component of the National Medical Device Evaluation System.

International Consortium of Orthopedic Registries:[30]
ICOR was launched in October 2010 to develop a strategic plan for establishing a distributed consortium of US and international registries. Representation includes nearly 30 total joint arthroplasty registries from more than a dozen countries, and there were consultations with the medical device industry, federal agencies including AHRQ, NIH and CMS, device regulatory agencies, device cataloging experts, payers, and the public. A critical and recurring theme has been the need for coordination and harmonization around data collection, measurement and analysis, including the challenge of classifying orthopedic devices captured in ICOR and methods for making meaningful comparisons between interventions.

Key Registry Attributes and Principles to Support a National System

Review of existing medical device registries provides examples of integration of many key attributes relevant to a national medical

Architecture of the Coordinated Registry Network: Integrating Unique Device Identifiers (UDI): The architecture to support medical device TPLC must by definition be end to end, with data flowing freely across a myriad of information systems associated with device and patient management. The data flow is initiated at the point of manufacture through assignment of a UDI to the individual device. Prior to implantation (throughout the distribution channel and supply chain), the UDI accompanies the device through inventory management. Upon implantation, device data becomes associated with the patient. Demographic, device, clinical and administrative data are associated and made available for device surveillance. Longitudinal data, typically acquired through clinical care processes and documented in the electronic health record, are collected and further associated with the device via data aggregation. The patient is followed through device explant or death, with the clinical and device performance data serving as the endpoint for evaluation of the device.

evaluation system, including 1) standardized definitions, 2) device and patient identifiers, 3) stakeholder subsets and deliverables, 4) informed consent strategies and 5) sustainable platforms. Table 2 provides a high-level summary of attribute strengths and weaknesses across these mature registry examples. At a glance it is evident that no single registry suffices for both surveillance and benefit/risk evaluation. It is equally clear that strategic linking across mature registries could create a flexible CRN approach which leverages strengths that significantly reduce or even eliminate weaknesses relative to the needs of a national device system. Thus the MDRTF recommends that evaluation of existing registries should concentrate on strong, mature attributes that might contribute to such CRNs within a National System. Weak or missing attributes in individual registries should be considered targets for strategic leveraging with other ready data sources but not necessarily as barriers to participation. A readiness assessment determines whether a given registry can successfully contribute to the medical device evaluation system and what attributes must be developed further to participate or to enhance participation. One component of this assessment should be whether or not a particular registry operates entirely on an autonomously sustainable model, or whether that registry would require additional resources in order to participate in a national device system.

Table 2. Strengths and Weaknesses of Existing Registries for Medical Device Evaluations

Strengths	Weaknesses
Device information exists in many registries. Several procedure- and disease-based registries include device information, even if the primary focus is not on the device.	Lack of sufficient detail to uniquely identify a device. While adoption of the UDI began in 2015, it is not sufficiently incorporated to serve as a unique key.
Detailed clinical information available. An extensive trove of clinical data is typically documented in registries, including clinical history, indications, procedure details and results, concomitant medications and adverse events.	Limited follow up. The observation periods of registries are typically time-constrained (e.g., until hospital discharge or a fixed time period).
Procedure-based registries capture initial device exposure. A procedure that includes device implantation often serves as the index (enrollment) event into a device registry.	Heterogeneous data formats, open architecture and inter-operability. Individual registries often lack the totality of the information required for medical device assessments. Patient-level information thus requires linkages to other registries, EHRs or claims data, especially to accomplish long-term tracking.
Relevant clinical outcomes. Outcomes of the procedure (or disease state) that are linked to the clinical outcomes are also associated with device exposure.	Lack of stakeholder value perception and of a calculable return on investment. Compelling incentives to accrue knowledge about the safety, benefit and risk profiles of medical devices are absent. A quantitative basis for contributing to medical device registries is lacking, thus reducing the priority and limiting the resources expended by those who manage these registries.
Contextual information collected. While device information is manually transcribed, the transcription process associates contextual data (date and institution of procedure, clinical characteristics, disease state, each associated with the device exposure).	Variable data quality. External data sources such as EHRs and claims data are themselves incomplete.
Clinical Trials Data Management Model. Information management model follows the clinical trial model of data abstraction and re-entry into dedicated database management systems (e.g., assessment of information management processes, data quality, statistical analysis and other aspects of information management).	Clinical Trials Data Management Model. Lack of seamless data capture integrated into the workflow with electronic data interchange into the registry: registries are typically not embedded into clinical care processes, making data contribution expensive and time-consuming
	Little attention paid to health care economics. Existing registries overlook real cost-benefit and comparative effectiveness calculus.

Chapter Summary Points

1. Even with the maturity of existing registries, much work remains to be done to create appropriately-targeted CRNs configured to address particular device-related questions of safety surveillance and/or benefit/risk.
2. Processes for the systematic collection of high-quality clinical data need to convert from a clinical trials information model to an informatics information model of data management, extracting data already embedded in the processes of care.
3. Adoption of both UDI and patient identification must become ubiquitous across the entire device life cycle, from point of manufacture through end of patient life. The UDI must be incorporated into the health information systems of healthcare enterprises, from point of entry in the supply chain through billing. Unique patient identification, whether via direct identifiers or via approaches that preserve privacy and resolve issues of informed consent while allowing for accurate patient matching, are critical in order to associate device follow-up and patient outcomes across most systems.
4. Device and clinical outcomes must be captured consistently and for a sufficient duration of follow up to meaningfully inform a longitudinal perspective.
5. Registry governance must recognize the intrinsic responsibilities of the public interest and population health as a component of its mission.

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Chapter III. Ideal Characteristics of a Coordinated Registry Network (CRN)

In the rapidly moving environment of informatics, registries and EHRs, optimal features of a National Medical Device Evaluation System will include the ability to both maintain quality and incorporate adaptive flexibility. Toward this end, for both near-term and long-term development, the MDRTF recommends the development of CRN approaches that mitigate individual registry deficiencies while providing the flexibility to address both safety surveillance and benefit/risk evaluation of specific medical devices.

The objective of a CRN is to overcome deficiencies in data from one source by leveraging another (e.g., patient-level linking of a procedure-based device registry with a registry containing long-term clinical follow-up). Optimizing such a registry network will require close attention to 1) the analytic objectives of the device evaluation posed, 2) the individual component registries or data sources (e.g., EHR, claims data, etc.) being linked to form the network and 3) the composite structure and content of the network.

The CRN will be no better than its weakest uncompensated component, in particular with regard to data quality issues. Such issues may include attributes such as missingness of data, use of non-standard or variable definitions or highly selected populations that limit generalizability. Thus the MDRTF considers it imperative to establish a checklist of basic minimum quality and content for both the components and the whole of such CRNs.

For the coordinated network to function, five basic principles can be identified.

Table 3. Optimal Attributes for a National Medical Device Evaluative System

1	Unique device identification information (ideally, use of the UDI)
2	Unique patient identification information to permit linkages across disparate information systems, including to EHRs or ambulatory data sets containing patient clinical characteristics and concomitant therapies
3	Longitudinal device-related performance information
4	Longitudinal patient outcome information
5	Surgeon, operator, or interventionist identification, along with institution location and date of device exposure

Principle 1. Ensure Ability to Identify Medical Devices

At least one registry should include medical device information relevant to the intent and purpose of the registry. At a minimum, devices should be identified to the level of granularity needed for assessing that device in all patients in the registry who have it. Ideally, UDI should be included.

Principle 2. Use Standardized Clinical Vocabularies, Common Data Elements, and Outcome Definitions as Required

Standardized data elements and definitions support the maximal flexibility for configuring CRNs within a national device evaluative system. Common data elements may be critical for aggregating larger cohorts from disparate data sources, or may be less essential when linking a procedure-related registry to a registry with long-term follow-up of the same patients.

Another aspect of this principle must be to recognize that device evaluation may have unique information requirements beyond the UDI and less generalizable than clinical outcomes, for instance the identity, training and experience of the procedural operator or technical details of the procedure or adjuncts used during the procedure.

Principle 3. Plan for Linking across Disparate Data Sources

Component registries and data sources within the CRN must support appropriate informatics strategies for interoperability. Such strategies may take different forms, including patient level data aggregation or distributed data networks or other common data model architectures. In the near term, strategies to leverage existing information resources should be the priority. For registries, EHRs or other data repositories being developed, their architecture should anticipate the need for data linkages and aggregation across multiple disparate sources.

Principle 4. Create Robust Governance

The MDRTF considers the primary principle of governance during the initial design and formation of any CRN to be one of stakeholder inclusiveness and collaborative good will. CRN governance will need to integrate existing governance structures already operational within each participating registry or data source. Broad stakeholder inclusion in the initial configuration of CRN governance structure is central to ensuring that the focus of both the networks and the national device evaluative system deliver the most value to the broadest range of interested stakeholders. While component registries within the network may have completed design features, strategic configuration of the CRN overall may target including component registries containing additional content or features of specific stakeholder interest (e.g., quality-of-life or cost information in addition to long-term clinical outcomes and device identifiers).

Principle 5. Develop Incentivized Sustainability

Existing device registries have been developed to provide specific deliverables to specific stakeholders (e.g., quality metrics collection to return to hospitals and practitioners). CRNs provide the opportunity, through strategically coordinated linkages, to greatly expand the range of deliverables and stakeholders with minimal incremental cost and work. This approach promotes a culture of incentive-driven device evaluation applicable to either safety surveillance or benefit/risk evaluation.

Sustainability of both participating registry components and the CRN overall is essential for a National Medical Device Evaluation System operating as a learning health system that adapts over time as data and knowledge accrue. Thus sustainability is critical to key applications, such

as recalibration of risk models for any particular device as designs and techniques evolve, or for the most efficient demonstrations that safety signals in a particular device class have been mitigated by targeted engineering successes in newer device iterations.

Relevant Historical Perspectives on Medical Device Registries

Within the past decade, multiple organizations have weighed in on the role of clinical registries for evaluating medical devices. While the current emphasis of the MDRTF on CRNs is novel, previous perspectives provide important insights for consideration and potential application in strategies of implementation. The clinical registry programs described in Chapter II illustrate the feasibility of some of these recommendations. A summary of these reports is in Table 4.

Table 4. The Role of Registries for Medical Device Postmarket Assessments

Institution	Strategy
Institute of Medicine (2010): *Public Health Effectiveness of the FDA 510(k) Clearance Process: Measuring Postmarket Performance and Other Select Topics*[1]	Leverage large, disease-specific clinical registries for monitoring device safety Create postmarket surveillance infrastructures to support extensible and iterative device data collection Utilize existing EHRs to facilitate meaningful device surveillance at the point of care, minimizing barriers to providers and delays in evaluation
Food and Drug Administration (2012): *Strengthening our National System for Medical Device Postmarket Surveillance*[2]	Utilize national and international device registries to bolster the national system for medical device postmarket surveillance Employ unique device identifiers Improve reporting and analytical strategies Develop novel evidence generation strategies
AdvaMed Registry Principles[3] (2013)	
Pew Charitable Trusts (2014): *Medical Device Registries: Recommendations for Advancing Safety and Public Health*[4]	Deliver timely, actionable information from registries to all stakeholders, including the public Streamline registry data collection through efficiencies that reduce the time and cost of reporting Use device registries to accelerate device innovation and to fulfill other regulatory responsibilities

Registry Design and Purpose

Typically the goals and purpose of a registry determine its design. For example, the purpose directly influences the number and type of patients, inclusion and exclusion criteria, risk factors, outcome variables and length of follow-up. Each of these elements should be clearly defined prior to data collection to assure consistency and high internal validity of the data. It is critically important to ensure that data definitions are harmonized with standardized definitions.

Inclusion of a particular registry into a CRN for device surveillance or benefit/risk evaluation may represent a significant shift from the original goals and purpose of the registry. Such inclusion

should not, however, preclude it from serving its original purpose. The goal of CRN structure, according to the principles enumerated above, is to enable the registry to both serve its original purpose and contribute to the National Medical Device Evaluation System—e.g., to serve "dual purposes" from a single workflow.

Ideally, all patients exposed to a medical device cancan be captured in a device registry. If only a subset of patients are available to inform a device evaluation question, the sampling strategy must be clearly defined. In addition, the target population must be precisely defined to understand the patients represented within the registry and the generalizability of its findings. The design of a long-term device registry must also have the flexibility to capture information on next-generation devices. A CRN provides alternatives to limited patient access and longevity over device iterations. For instance, if device data captured from a closed system such as the VA leaves questions about generalizability, a CRN could be constructed to augment the VA's national EHR by linking to comparable information from a different health system or a professional society registry such as NCDR.

Both device registries being newly designed and CRN structures are likely to contribute importantly to regulatory decisions. To carry out this role, close collaboration with FDA is essential in both the design and maintenance stages. The Task Force recommends that FDA representatives be consulted regarding specific data elements to be collected, associated definitions and reporting formats likely to be used for regulatory decisions., as well as for insights into the adequacy with which strategically coordinated registry networks can orchestrate solutions to otherwise concerning limitations related to the individual participating registries for evaluative purposes.

Data Security

Health information privacy is a national high priority. Systems intending to access, compile or share such information across disparate data sources must involve expertise in data security. The data in particular clinical registry programs may be collected from electronic medical records or submitted under contracts with professional societies or other entities. In configuring CRNs, a variety of combinations of contracted entities and obligations may be encountered. Thus in addition to informatics expertise ensuring data security, legal expertise should be engaged early in the CRN development process.

Data Access

Issues of data access include aspects ranging from audits ensuring data quality to oversight of data analysis, interpretation and reporting. Data access issues also include fairness and transparency. Issues such as timeliness may vary depending on whether a potential safety signal has been detected or whether less urgent observations are being reported for academic purposes.

Existing device registries created with purpose and objectives will generally have established structure defining data access by registry leadership, registry sponsors or other interested

parties. When such registries participate in CRNs they begin to serve a dual purpose in conjunction with other participating registries or data sources, and their pre-existing data access processes will likely require both technical and some governance modifications. The MDRTF recommends that, when possible, the participating components and registries have representation within the CRN and vice versa

As the CRN construct is intended to augment the National Medical Device Evaluation System's ability to promote value and deliverables to stakeholders, success will bring with it novel issues related to data access. Thus in addition to the involvement of leadership from component registries, the MDRTF recommends that stakeholders also be engaged regarding data access early in the development of the CRN.

Certain special issues regarding data access are predictable in a system intended to participate in regulatory decisions and best practice guidelines. For instance, data will be collected across devices from multiple manufacturers. Ensuring that brand-specific data is analyzed and interpreted responsibly is critical both to competitive industry participation and to accurate and informative accrual of device benefit/risk and safety profiles. One approach could be to provide participating manufacturers with specific device information related to their devices while otherwise providing only aggregate data. Other options may be entertained, as industry is likely to have unique research needs appropriate for design, marketing and future regulatory studies. Coordination between industry and CRN leadership will be essential to collaboratively and appropriately meet the expectations of all stakeholders. In many cases the MDTRF believes that industry representation should have a role as a full partner in CRN governance structure.

Data Analysis

CRNs should establish processes and standards for creating data analytic files and maintaining them to support quality improvement, research, regulatory reports, public reporting and industry requests. Traditionally registries not only have established some such processes but also have statistical expertise available applicable to the original design and objectives of the registry. CRN participation affords a novel opportunity to include methodologists from multiple stakeholders in constructing analytic approaches to data accrued from disparate sources. Such intellectual collaboration across a National Medical Device Evaluation System could promote unique approaches to safety signal detection, benefit/risk calculation, causal inference and many other key areas of interest. These directions are further highlighted in Chapter V of this report.

Dissemination of Information

For the many efficiencies of CRNs built on dual purposing existing registries, performing and disseminating analyses that provide novel deliverables to a broad range of stakeholders will add both work and cost. As the information reported and shared through these processes constitutes one of the most important aspects of a National Medical Device Evaluation System, the MDRTF strongly recommends finding support for added expense in this area in particular. Furthermore, the Task Force points out that even with the added cost of leveraging a CRN data

source for analyses pertinent to many stakeholders, the efficiency of drawing multiple sets of information from a single source still constitutes considerable opportunity for savings in research and development timelines and cost for new devices.

Similarly, CRNs will need to transparently address that what information is disseminated, when it is released and how it is communicated may need to vary across stakeholders. For example, with the first concerns about a potential safety signal, regulatory authorities need immediate notification. Patient or practitioner release, however, may be more appropriate once the signal has been confirmed as real.

Further aspects of information dissemination are addressed in Chapter VI in relation to governance structures.

Governance

Governance of the CRN is considered in Chapter VI. Governance is a critical consideration for any registry or activity involving data exchange, such as for a registry participating in a CRN. Without a transparent and accountable governance process, the risks of misalignment with purpose (including dual purpose) and data quality problems is high. A successful governance effort depends on several factors: clear roles and relationships should be defined (including those of any external sponsor); there must be rules for data access and use; safety and efficacy should be primary concerns for analytic capabilities; focus should remain on the needs of end users; end users should be represented on the governance body.

All relevant stakeholders should be represented and have the opportunity to escalate items for further discussion and adjudication. The structure of both the governance body and the registry should be publicly available as should the names of the board or executive steering committee(s). Subject matter experts should participate regularly, and their identities and affiliations should be disclosed along with those of senior staff. External review and audit committees should provide oversight, audits, and independent data analysis. The governance body and activities should coordinate with a stakeholder advisory committee. Criteria should be established to identify and manage conflicts of interest. All conflicts of interest should be disclosed and a process should be in place to remove individuals whose conflicts threaten impartiality.

Collaboration with FDA, Manufacturers, and Other Stakeholders

As registries evolve to support medical device evaluation, collaboration with multiple stakeholders becomes increasingly important. At a minimum, it is essential that they collaborate with FDA, sharing either the results of their device evaluation efforts or data under formal agreements. There should also be efforts to develop bi-directional collaboration with manufacturers to optimize information exchange about potential device safety issues. Additional stakeholder collaborations, including with patient and consumer groups and other entities, may also be essential for success. For registry programs that become involved in the

execution of pre- and postmarket studies (e.g., post-approval studies), collaborations between the registry program, FDA and industry are mandatory.

One of the major functions of a device registry participating in a CRN will be to collect and analyze information that can be used for regulatory studies and evaluations. A clinical device registry should be able to accomplish that – and do it faster and less expensively than traditional manufacturer registries, which are often one-off entities. For clinical registries to be effectively used in this way, however, regulatory studies should be amended in concert with FDA to exploit the advantages of device registry infrastructure without compromising the regulatory science under study. In the TVT Registry, for example, a current post-approval study (PAS) does not rely on traditional strict inclusion/exclusion criteria for patient selection. Instead, the study takes advantage of the real-world nature of TVT Registry data and defines the study population as a set number of consecutively enrolled patients.

FDA has begun to work with industry and device registries to design regulatory studies that take full advantage of device registry strengths. This concept, known as "comprehensive registry-based surveillance with shared responsibilities," is still in the early stages of development. The Task Force recommends that FDA continue to develop this concept of adapting regulatory studies to exploit the strengths of device registries, as adaptation of study designs to registry or CRN composition and adaptation of CRN composition to study design needs are both likely to promote the evolution of the most optimal National Medical Device Evaluation System.

Sustainability

The ability to adequately fund a registry is vital to it meeting its intended goals and ultimately providing value to its stakeholders.[5] In addition to costs associated with initial data capture, those who operate registries must plan for data management and operating costs to ensure high data quality and usability of the registry as a valued resource. As an example, the Australian Commission on Safety and Quality in Health Care funds infrastructure development, data cleansing, reporting and analysis of quality of care based on succinct datasets captured routinely by clinicians at the point of care[6]. The current reliance on professional societies or other independent groups to be responsible for registry design and development and to bear responsibility for these major operational costs will not result in long-term sustainability of a National Medical Device Evaluation System. Because costs are high and funding sources are limited, device registries are routinely designed to meet the narrow purposes of a limited stakeholder group for a time-specified period. Device manufacturers, for example, may participate in registries as a condition of device approval by a regulatory authority such as FDA. In other examples, participation in a registry by a healthcare provider could be a condition of reimbursement required by CMS or other payers. When registries are used to meet specific regulatory, payment or research requirements the result is often fragmented, built upon proprietary infrastructures with short-term goals, limited data and little value beyond the initial population, device type and research questions.

Long-term sustainability can be achieved by demonstrating value to a broader base of stakeholders. This objective will fit strategically CRNs more than individual registries. CRNs will be more able to show more comprehensive ability to capture data efficiently, to detect device safety signals and their mitigation, to demonstrate device performance across device types for comparative effectiveness analysis and to provide data about long-term outcomes. The sustainability and retention plan should be part of the overall registry governance structure, which can then be integrated into a CRN structure. Those parts of the governance responsible for sustainability provide guidance and oversight to ensure reduced registry costs, to optimize the spread of the financial burden and to provide leadership and guidance toward greater long-term value for multiple stakeholder groups.

Registry Utility over the Total Product Life Cycle (TPLC)

Different evidence needs across the TPLC may be addressed by leveraging registry capabilities and data. Intrinsic to the TPLC concept is the continuous accrual of safety and benefit/risk information, as the early generations of devices promote the engineering of better and safer iterations. Contemporary applications, however, tend to address the TPLC in discrete and relatively independent milestones, often using new definitions and new case report forms at each stage of device evaluation. While reasonable for business models centered on market entry and postmarket uptake, this trend incorporates redundant costs and time delays and, through fragmentation, undermines data poolability and the real accrual of knowledge, especially regarding rare safety concerns. Historically this approach is one of the forces shaping the limitations of modern stand-alone registries.

Leveraging and linking registry infrastructure through sustainable CRNs promotes ongoing device evaluation with more robust accrual of benefit/risk information while reducing costs and timelines associated with TPLC milestones. Ongoing device registries that have standardized outcomes and definitions, data entry formats with which sites are familiar, and longitudinal data with standard-of-care comparators support CRNs that can provide more informative analyses while expediting clinical trials or other evaluations. From the perspective of the Task Force, identifying the strengths of registries ideal for participation in CRNs centers on their ability to promote linking critical information across discrete stages of the TPLC to enhance continuity and a more informative assessment of benefit/risk.

Registries should be designed to avoid the one-off approach to regulatory studies. Each class of studies has a common set of data elements and analyses. Working with FDA, device registries should identify the core data elements and standardized definitions essential for regulatory studies within a range of devices. For example, a core set of data elements could be specified for all TAVR post-approval studies. Registries cancan then develop a core PAS data collection module with submodules to accommodate unique data elements for specific devices. This registry design should streamline the existing regulatory study paradigm and produce results more quickly at reduced cost. Device registries should be encouraged to develop core IT modules to capture this information as structured data sets in order to minimize duplication, redundant data collection and cost.

Registry Applications toward Premarket Evidence Requirements

Depending upon the risk classification of a medical device, clinical data regarding its safety and effectiveness may be required as part of the premarket review process. Such data, collected under an Investigational Device Exemption (IDE), typically result from prospective studies with well-defined protocols and statistical analysis plans, and are frequently randomized and controlled. Where there is sufficient historical information on the performance of comparative devices, objective performance criteria (OPC) may be established as the comparison. OPC are "performance criteria based on broad sets of data from historical databases (e.g., literature or registries) that are generally recognized as acceptable values and may be used as surrogate or clinical endpoints in demonstrating the safety or effectiveness of a device."[7]

Registry data may be used to develop OPC for a device providing the data are reliable and complete, include appropriate data elements to assess safety and effectiveness and reflect usage of the historical products in comparable populations and across applicable geographies. Leverage of registry data to develop OPC should focus on identification, incidence rate and timing of safety risks to help establish the balance of data required for product approval vs postmarket surveillance. In some cases registry data may also be useful to leverage performance or effectiveness study design as well, for instance in providing informed priors for Bayesian models. Any registry used for OPC must reliably capture adverse events.

Premarket studies to demonstrate the safety and effectiveness or benefit/risk of a medical device must define superiority or non-inferiority relative to an existing comparator, either through randomization or well-constructed comparator cohorts. Some registries may provide infrastructure suitable for such premarket designs. Registry-based randomized controlled trials (RCTs) may be imbedded into active registry infrastructure. In such applications the registry provides an electronic data capture system with efficiencies such as site familiarity and existing workflow, existing quality metrics and existing definitions and data dictionaries, eliminating the need to build novel case report forms and train sites in their use. As premarket studies (Table 5), such registry-based RCTs still must be conducted according to 21CFR 812, be approved by FDA and fulfill requirements related to IRB/Ethics Committee (EC) approval, informed consent, data collection and management, data integrity, investigational site monitoring, investigator and sponsor responsibilities, adverse event reporting and submission of periodic reports to FDA and IRBs. The role of registries in the conduct of randomized trials has recently received attention. In the randomized registry trial (RRT) concept, the use of registry data greatly reduces study costs and time while providing larger patient cohorts and real-world information. The RRT concept appears to have considerable potential in device studies, so an ideal registry will have a firm understanding of RRT principles as well as practical experience conducting studies of this kind. Where ideal registries do not exist, CRN structure may be critical to expanding the impact of RRT designs for premarket as well as postmarket studies.

Leveraging Registries for Postmarket Evidence Requirements

Following premarket approval a device may be commercialized for the instruction for use (IFU) indication applied to the population for which it is intended. At the time of approval, there may

be residual concerns, especially safety concerns, such as very long-term safety or the generalizability of the premarket outcomes data—e.g., the ability of smaller community sites or operators to achieve results similar to those attained by experienced research centers that participated in the pivotal trial. Furthermore, once the device is released, physicians may elect to use it off label as a dimension of the practice of medicine. With truly innovative or breakthrough technologies, the postmarket may require condition-of-approval studies, may provide an opportunity for labeling extension IDE studies and will be a critical arena of ongoing concern for rare but important safety signals. Promoting national and international registries for selected products and developing and pursuing new methods for generating, synthesizing and appraising evidence is part of FDA's plan to strengthen the national system for medical device postmarket surveillance. The MDRTF recommendations for CRNs and the optimal characteristics of their participating components are intentionally aligned with the strategic approach of the FDA's plan for postmarket surveillance of devices using registry infrastructure.

Table 5. Recommendations for Premarket and Postmarket Application of Device Registries

	Premarket	**Postmarket**
1: Protocol	A well-designed protocol, reviewed and approved by FDA with clearly defined safety and effectiveness endpoints should exist. The possibility of embedding the premarket study within the registry should be discussed with FDA as soon as possible and the planning of the study should include the registry owners, the sponsor and FDA. Operational representatives from the registry may also be included in the discussions. Consensus should be reached on study design, standardized definitions for adverse events and recommendations for endpoints that reflect appropriate device-, procedure- and patient-related safety and effectiveness measures.[8]	A well-designed plan for collection, review and analysis of key data elements which is approved by FDA (and other stakeholders as appropriate) should exist. The main elements of the protocol should be developed by key stakeholders, including FDA, the registry owners, sponsor and professional societies and CMS as appropriate. Consensus should be reached on how data will be collected, which harmonized data elements will be collected, standardized definitions for adverse events, duration of the study and appropriate time periods for patient follow-up.
2: Protocol	Should include the comparator group, whether OPC or prospectively identified. If randomized, the randomization process and schedule should be described. The protocol should include a statistical analysis plan that identifies the analyses (including planned subgroups and missing data algorithms) and comparisons that will be conducted. Rules for pooling data from different registries should be agreed upon a priori.	Should include a statistical analysis plan that identifies the analyses (including planned subgroups and how to handle missing data) and comparisons that will be conducted. Rules for pooling data from different registries should be agreed upon a priori.
3: Adding elements	The registry must have the capability to add data elements as required by the substudy protocol. Alternatively, the registry may directly populate data elements that are a sub-section of a larger part 11 compliant data	If using an existing registry, it should have the capability to add data elements as required by the study plan or have open architecture through which key data elements can be electronically exported

	Premarket	Postmarket
	system.	to a larger primary database. If using the same registry as that used for the premarket study cohort, the registry should have the ability to continue to follow that cohort.
4: Version control	There should be processes and procedures related to version control of all study-related documents.	There should be processes and procedures related to version control of all study-related documents.
5: Ethical issues	Appropriate processes and procedures related to the protection of human subjects (including privacy, informed consent, data security and ethics according to local, national and international regulations) and the approval of applicable oversight committee(s) (IRB, EC, privacy, etc.) should be in place. All subjects enrolled in the IDE study must be consented to participate in clinical research and understand that they may receive an investigational device and that their protected health information (PHI) may be shared with the sponsor and regulatory agency.	Appropriate processes and procedures for protecting human subjects (including privacy, informed consent, data security and ethics according to local, national and international regulations) and the approval of applicable oversight committee(s) (IRB, EC, privacy) should be in place.
6: Data compliance	The computer systems used to collect and analyze the data must be 21CFRPart11 compliant. The systems must be validated to meet FDA requirements for electronic records and signatures.	The computer systems used to collect and analyze the data must be 21CFRPart11 compliant. The systems must be validated to meet FDA requirements for electronic records and signatures.
7: Follow-up procedures	A process for patient follow-up should be in place.	A process for patient follow-up should be in place.
8: Adverse event reporting	Adverse event (AE) reporting, including serious adverse events (SAEs) and unanticipated adverse device effects (UADE), should be in place. Timely reporting of events to the sponsor for further investigation and to regulatory bodies (FDA) and IRBs/ECs is essential. Sufficient information regarding the AEs (including relatedness to the device and/or procedure), should be provided to the sponsor to allow for investigation and analysis. The process should be coordinated with the safety management plan defined in the protocol.	Adverse event reporting, including SAEs and UADE, should exist and enable timely reporting of events to the sponsor for further investigation and compliant reporting to regulatory bodies (FDA) and IRBs/ECs. Sufficient information regarding the AEs should be provided to the sponsor to allow for investigation and analyses. The process should be coordinated with the safety management plan in the protocol.
9: Site compliance	Processes and procedures must insure site compliance with the protocol, good clinical practices (GCP) and data integrity and validity including routine site monitoring.	Processes and procedures must insure site compliance with the protocol, GCP and data integrity, validity, and quality.
10: Governance	Clear agreements on access, use and ownership of data between the registry, the sponsor and the regulatory body should be in place.	Clear agreements on access, use and ownership of data between the registry, the sponsor and the regulatory body should be in place.

The postmarket stage of the TPLC, both near term and in a longer term vision of a national device evaluation system, can be seen as the locus of both clinical practice and health care economics. Linkages between ongoing device registries may include disease states (e.g., diabetes) in which the benefit/risks of devices may cross over evaluations of new drug strategies or other clinical practice changes over time. At an even broader level, the degree to which device benefit/risk may be similar to other medical strategies but involve cost differences—to patients, payers or the health care system—points to the need for a national device evaluation system leveraging registries to accommodate patient-centric and comparative effectiveness calculus beyond the new device benefit/risk. Registries that give insight into practice patterns, health care costs and outcomes, may provide the best basis for more robust CRN support of clinical practice guidelines as well as the option to track adherence to such guidelines through the same registry-based CRN infrastructure.

Mandated Postmarket Studies

A PAS is frequently a condition of device approval. That study may continue to follow the cohort of subjects who received the investigational product as part of the IDE or may involve new subjects who received the device after the product had been approved for marketing, or a combination of both. The protocol for the PAS is typically developed by the sponsor with close input from FDA. The size, duration, follow-up requirements and end-points are determined based upon the risk profile of the device. FDA has encouraged the development of registries to fulfill PAS requirements for some Class III products, including breast implants and transcatheter aortic valve implants (TAVI).

FDA may also mandate a postmarket surveillance study after a medical device has been marketed when a significant public health issue has arisen (per section 522 of the Food, Drug and Cosmetic Act). As with the premarket evaluation, the Task Force recommends the items listed in Table 5 when using registries and registry-based CRNs to fulfill mandated postmarket study requirements.

Chapter Summary Points

1. An ideal device registry is designed to function not only as a stand-alone entity but also as one element in a landscape of linked registries and other data sources as a strategically CRN.
2. Five principles guide CRN functioning (1) Ability to identify medical devices, (2) use of standardized clinical vocabularies, common data elements and outcome definitions (3) Plans for linking across disparate data sources, (4) Creating robust governance, and (5) Developing incentivized sustainability.
3. CRN structure and governance must meet the needs of multiple stakeholders including patients, clinicians, healthcare systems, FDA, registry owners, and industry partners.
4. Leveraging and linking registry infrastructure through sustainable CRNs promotes ongoing device evaluation with more robust accrual of benefit/risk information while reducing costs and timelines associated with TPLC milestones.
5. CRNs can play a critical role in pre- and postmarket studies for regulatory decision-making.

Pilot Projects

Project I

Registry Accreditation Develop registry standards and apply to existing national, professional, state, regional, and institutional registries to determine where there are current gaps that need to be addressed for linkage and surveillance and to determine the feasibility of registry certification/accreditation.	
1. Disease/ device focus	Cardiac, Orthopedic, and Vascular devices
2. Immediate research question(s)	Define the minimum standards for inclusion in a CRN and apply to existing national, professional, state, regional, and institutional registries in order to validate and identify gaps that need to be addressed for linkage and surveillance
3. Stakeholders engaged	Patients, clinicians, healthcare systems, registry owners, FDA
4. Existing national resources leveraged	National, professional, state, regional, and institutional orthopedic, cardiac, and vascular registries
5. Efficiencies promoted	Prioritization and selection of high quality registries for inclusion in a CRN optimizing data integrity for national surveillance
6. Applied national standards & definitions	Integration of AHRQ registry handbook, Pew, and AdvaMed principles

Project II

Guidance Document Develop a detailed guidance outlining steps and key concerns to address to utilize registry infrastructure for collection of data to support market approvals and to fulfill postmarket data requirements.	
1. Disease/device focus	Cardiac, Orthopaedic, Vascular, Ophthalmic devices
2. Immediate research question(s)	How can registry infrastructure be leveraged to collect data needed to support products throughout the total product life cycle, with particular focus on premarket and post-approval regulatory requirements. What lessons can be learned and generalized from the use of the TVT registry for continued access protocol (CAP), TAVR alternative access IDE, post-approval studies, and of the Society for Vascular Surgery's VQI PSO for post approval studies.
3. Stakeholders engaged	FDA (and other regulators), registry owners, industry, clinicians, patients
4. Existing national resources leveraged	National, professional, state, regional, and institutional orthopedic, cardiac, and vascular, ophthalmic registries
5. Efficiencies promoted	Standardization of process and considerations for industry/researchers/regulators to guide discussions on use of registry infrastructure to collect data for regulatory requirements. This will result in the more efficient conduct of clinical trials at reduced cost
6. Applied national standards & definitions	Draft FDA Guidance Document "Balancing Premarket and Postmarket Data Collection for Devices subject to premarket approval

Project III

Integration of Procedural and Claims Data with Other Electronic Data Develop a detailed guidance outlining steps and key concerns to address to successfully integrate available electronic data for regulatory and reimbursement decision making	
1. Disease/device focus	Cardiac, Orthopaedic, Vascular, Ophthalmic devices
2. Immediate research question(s)	What is required for the successful integration of data from multiple sources for regulatory and reimbursement decision making. In 2014 CMS issues a national coverage determination for nonsurgical, transcatheter mitral valve repair and made participation in a national registry a condition of coverage. What lessons can be learned and generalized from the linkage of the TVT registry to the CMS claims data. Are there other examples of integration of multiple sources of electronic data (perhaps Michigan state based registries supported by BCBS or Health System registries like Kaiser), and, if so, how does that compare to the TVT experience
3. Stakeholders engaged	FDA (and other regulators), CMS (and other payers) registry owners, industry, clinicians, patients
4. Existing national resources leveraged	National, professional, state, regional, and institutional orthopedic, cardiac, and vascular, ophthalmic registries, claims databases (CMS or private payers), EHRs
5. Efficiencies promoted	Standardization of process and considerations for all stakeholders to guide discussions on integration of data from multiple sources in a meaningful way to inform regulatory and reimbursement decisions. Use of registry infrastructure to collect data for regulatory requirements.
6. Applied national standards & definitions	

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Chapter IV. Priority Medical Device Opportunities

High-risk devices represent the most important focus for registry development, as clinical trials for such devices (e.g., metal-on-metal hips, cardiac stents, or implantable defibrillators) often involve few patients. Implanted devices and devices that enable major interventional procedures may entail a particular need for large registry-based populations and longer-term observation. For some implants, linking the registry to CMS data may provide sufficient information about long-term performance. Registries may prove particularly valuable when existing electronic data sources, administrative data sources, adverse event reporting, and postmarket studies are likely to be inadequate or uninformative.

The principles below are partially informed by the 2013-2014 series of meetings held collaboratively by the Medical Device Epidemiological Network (MDEpiNet) Science Infrastructure Center at Weill Cornell Medical College, Pew Charitable Trusts, and the Blue Cross and Blue Shield Association (BCBSA). These guiding principles are focused on but not limited to implants.

Guiding Principles for Establishing Device Registries

1. The consequences of device failure have serious implications for the public health, and include serious disability or death. This is not limited to circumstances when premarket studies have shown a positive benefit-to-harm profile for the device.
2. Rapid uptake of the device is expected and adverse events are likely to be rare but very serious. High rates of unanticipated adverse events may occur when a broad population is exposed to the device. If the registry infrastructure is in place, data may be available quickly to evaluate the harm.
3. The device uses new technology whose long-term safety and effectiveness are not well understood. Technological advances can lead to innovative, first-of-a-kind devices as well as incremental improvements to existing devices. In some cases, the short-term effect of the device has been well-studied but its long-term impact is unknown. This is particularly important when the consequences of device failure are serious. Registries can provide information on the long-term performance of the device and the health impact on patients.
    a) Many devices require further postmarket studies because they will be used for a longer period than the patient follow-up interval from the premarket pivotal trial.
4. The device type has substantial design variations. When there are many types of a given device, the potential exists for significant variation in outcomes to emerge. Capturing outcomes in a registry would allow for comparative assessment of performance. Ultimately, data on outlier performance (either good or bad) could inform clinical treatment. Some examples include hip and knee devices. These devices are produced by multiple manufacturers, have a wide range of designs, and use different materials. Comparative effectiveness data on their long-term performance would have tremendous value to all stakeholders. In these cases, it is important for the performance of all of the devices to be captured in the same registry. In circumstances where each registry captures only one type of device, combining those disparate data might not be straightforward.

Such a practice will impair the goal of comparing the performance of different devices and increase the burden of registry data collection and decrease its sustainability while also leading to duplicated effort and additional costs in money and time. Multiple registries could make the long-term sustainability of the effort more challenging if registry funders and those relying on the data are uncertain as to which registries provide the best information and how to access it.

5. The performance of the device may vary significantly across the population. Clinical trials conducted for marketing approval generally have strict inclusion and exclusion criteria, and marketing approval is based on device performance in that limited population. After marketing approval, the patient population may differ substantially from the study population, and these differences may have important health implications.
6. The safety and effectiveness of devices can differ in men and women. In general, women have higher bleeding rates and procedural morbidity and mortality than men, which means that the risk for many medical devices can differ by sex. If a device is expected to have significant uptake among those 65 and older, but those populations were not well-represented in the premarket study, the registry can collect information on this important subpopulation. A postmarket registry can confirm that the device is still safe and effective when used in a wider population and evaluate device performance in subgroups. The registry could also identify risk factors that affect the performance of the device.
7. The outcome of the procedure (in the case of implanted devices) is highly dependent on operator performance. In contrast to drugs, patient outcomes can be affected by operator skill and training. For some devices, there is likely to be a relationship between patient outcomes and procedure volume (by both the provider and the facility). Collecting data from a wide range of providers will present a more complete picture of the real-world performance of the device than is possible in a small randomized controlled trial with a limited number of highly-trained investigators. The information on operator experience can be used to understand whether training programs are adequate and needed. Additional study through a registry may demonstrate that a base level of training is necessary in order for any provider to become proficient with a device. Alternatively, for some devices, the amount of training could vary from provider to provider. In this case, participation in a registry could show when a provider has achieved proficiency or how many procedures are adequate.
8. The total costs of the device are substantially higher than current therapy. As a new, expensive technology is introduced into the medical device market, payers and hospitals may need more information on outcomes and quality of care associated with the new therapy compared with standard care.
9. More specific information is needed to establish best practices for the device, particularly when off-label use is expected, and there are substantial legal implications. There are hospital, operator, and patient-level interactions that might need to be considered for establishing best practice and understanding the incentives for, as well as the impact of, off-label use.
10. Unanticipated problems with similar devices were identified through premarket review, passive adverse event reporting, or postmarketing studies.
11. The devices require significant patient interaction to collect patient-centered outcomes.

These guiding principles should be viewed from the perspective of the public health value that registry data could provide. In some cases, just one unanswered scientific question might justify the use of a registry, but the argument for a medical device registry becomes more compelling with each additional scientific question.

From a clinical perspective, we have focused on implanted devices and devices that enable the conduct of major interventional procedures by reviewing several national resources:

- Institute of Medicine report on comparative effectiveness research (CER) and list of 100 initial CER priorities[1,2]
- CMS MEDCAC meetings from the outset (1999)[3]
- Frequency of procedures/device use[4,5]
- FDA medical device adverse event reports and device safety communications[6]
- US Burden of Disease Collaborator study[7]
- Analysis of FDA Advisory Committee Meetings[8]

The priority areas include the following devices and procedures:

1. Hip replacement devices
2. Knee replacement devices
3. Vascular procedures/devices (includes peripheral, AAA, carotid and vascular access/catheters)
4. Spine surgery procedures/devices
5. Cardiac valve replacement
6. Atrial fibrillation ablation procedures/devices
7. ICD/cardiac resynchronization therapy (CRT) implantation
8. Coronary stents
9. Robotic and other less invasive surgery
10. Ophthalmic procedures/devices
11. Surgical mesh

Table 6 shows the volumes and total charges associated with these priority areas.

Table 6. Weighted Number of Hospital Stays, Median Charges, and Total Charges for Hospitalizations Involving Each Priority Procedure or Group of Procedures in the US 2012 National Inpatient Sample.

Procedure(s)	Estimated no. of Stays Involving Procedure	Median Charges per Hospital Stay (IQR)($)	Estimated Total Charges for Hospital Stays in 2014($)
Hip Replacement/ Resurfacing	423,195	49,647 (36,557-69,262)	24,169,781,944
Knee Replacement	634,354	46,470 (34,481-63,736)	33,080,495,756
Vascular Procedures	197,760	75,659 (46,812-123,740)	20,720,880,348
Carotid Stenting	16,075	50,131 (34,791-79,951)	1,135,748,765
Peripheral Vascular Stenting	154,575	75,152 (45,896-125,803)	16,596,388,267
Endovascular AAA Repair	31,715	94,784 (67,772-136,408)	3,614,610,207
Spine Surgeries	451,155	78,029 (49,157-125,501)	46,375,696,105
Spinal Fusion	445,255	78,257 (49,333-125,936)	45,922,412,471
BMP	80,115	100,230 (66,975-153,440)	9,995,958,729
Disk Replacement	3,720	64,078 (40,649-98,080)	297,952,989
Robotic-Assisted Surgeries	111,500	41,939 (29,433-62,131)	5,803,586,279
Aortic or Mitral Valve Surgery	104,445	156,611 (107,958-242,384)	21,483,405,944
Catheter Ablation (AFib)	65,250	85,660 (58,021-123,130)	6,719,715,076
ICD or CRT Devices	77,285	138,009 (95,205-199,736)	12,526,390,801
Coronary Stenting	535,780	62,668 (44,636-92,011)	42,169,819,952
Robotic Mitral Valve Plasty	940	116,764 (88,417-177,924)	151,068,552
Robotic Lobectomy	2,575	83,157 (59,860-114,886)	246,934,098
Robotic Esophagectomy	200	111,625 (82,278-196,757)	33,488,013
Robotic Thymectomy	265	54,116 (34,317-80,951)	17,937,992
Robotic Hysterectomy	39,215	37,230 (26,304-54,734)	1,747,290,122

Procedure(s)	Estimated no. of Stays Involving Procedure	Median Charges per Hospital Stay (IQR)($)	Estimated Total Charges for Hospital Stays in 2014($)
Robotic Nephrectomy	14,860	47,860 (34,764-69,974)	879,073,988
Robotic Cystectomy	2,095	101,300 (70,137-144,077)	254,699,296
Robotic Prostatectomy	45,140	39,684 (28,605-54,333)	2,025,653,640
Robotic Proctectomy	2,390	67,475 (45,448-104,342)	206,553,173
Robotic Colectomy	4,560	56,958 (39,317-82,300)	323,285,934
Laparoscopic/VATS Surgeries	141,995	44,421 (29,647-68,652)	8,417,406,156
Thoracoscopic Lobectomy	11,545	61,063 (44,327-90,225)	902,053,209
Thoracoscopic Esophagectomy	195	175,568 (101,229-305,391)	49,020,141
Thoracoscopic Thymectomy	265	45,043 (27,870-78,274)	16,601,667
Laparoscopic Hysterectomy	30,790	30,205 (20,638-45,457)	1,116,757,999
Laparoscopic Nephrectomy	7,025	43,102 (30,896-63,437)	397,436,577
Laparoscopic Cystectomy	70	108,997 (72,453-166,305)	9,153,571
Laparoscopic Prostatectomy	405	35,517 (24,259-47,413)	17,643,711
Laparoscopic Proctectomy	2,675	58,468 (41,348-90,335)	206,044,882
Laparoscopic Colectomy	89,595	47,641 (32,486-72,933)	5,761,463,710

Hip Replacement

Experiences with metal-on-metal ASR™ implants made by DePuy Inc. as well as recalled metal-on-metal implants in general are changing our framework for medical device evaluation.[9-13] The failure of metal-on-metal hips was one of the main debacles that led to recognition of postmarket surveillance needs. Registry-based investigations of these failures, including the development of the ICOR, helped reveal and quantify the problems with hip replacement devices.[14-16]

Systematic reviews have shown the limits of clinical trials in this field[17] and the need to investigate head size, bearing, and cementing techniques. While most new devices were not

found to have any advantages over older products,[18] there are examples such as the highly crosslinked polyethylene (HXLPE) inserts that have shown promising results regarding wear in RSA studies.[19,20]

Importantly, there are thousands of combinations of devices available on the market in the United States, and many approved devices differ from those used internationally. Within the US, the Kaiser Permanente Total Joint Replacement Registry is the best-established registry based on an integrated delivery system, with data on over 148,000 joint replacements collected over 10+ years. This registry has been used to address many important device safety questions in recent years.

There is also a growing number of state registries established in the past few years, including the American Joint Replacement Registry (AJRR), which was launched in 2009. The AJRR is certified by the Centers for Medicare & Medicaid Services (CMS) as a Qualified Clinical Data Registry in 2014. The AJRR is a multi-stakeholder initiative and also owns and manages the California Joint Replacement Registry (CJRR). The AJRR procedural dataset includes information from other large institutional registries, such as HealthEast Joint Replacement Registry, the Connecticut Joint Replacement Institute, and the Harris Orthopaedic Lab at Massachusetts General Hospital. The registry has sustainability hurdles to overcome and has been mostly funded by manufacturers.

The Function and Outcomes Research for Comparative Effectiveness in Total Joint Replacement (FORCE-TJR) registry has data on more than 24,000 patients treated by a diverse and representative group of surgeons, and hospitals in 24 states (urban and rural; academic and community hospitals; low- and high-volume practices) to date and is an important resource for device safety and effectiveness studies.

A national registry or existing registries organized as a CRN can provide a foundation for a postmarket surveillance system that can help reveal promising or harmful technologies and assist manufacturers, regulators, surgeons, and patients in identifying the most promising devices.

Knee Replacement

While hip replacement devices have been under scrutiny, there are growing concerns related to knee replacement, which is performed twice as frequently as hip replacement in the US. A major systematic review reported no advantages for recently introduced knee replacement technologies and possible harms associated with some of these devices.[21]

Recent findings from ICOR related to mobile knee devices and posterior-stabilized devices have shown that there are many frequently used devices with inferior performance. The ICOR studies addressed several technologies such as various mobile-bearing devices within the context of both posterior stabilization and non-posterior stabilization (cruciate-retaining). In non-posterior-stabilized implants, an ICOR study of the effect of mobile versus fixed-bearing found over 40% higher risk of revision surgery associated with mobile bearings.[22] In another study of mobile

bearings, patients receiving posterior-stabilized knee devices (17.6% patients worldwide) had inferior outcomes compared with those receiving fixed devices.[23] A third ICOR study of knee implants compared fixed posterior-stabilized implants with fixed non-posterior-stabilized implants (cruciate-retaining)[24] and found that posterior-stabilized devices are associated with much higher risk of revision than non-posterior-stabilized devices in patients without patellar resurfacing. There are also questions related to short- and long-term outcomes of patella resurfacing.

There are thousands of combinations of knee devices available on the US market. A national registry in this field is critically important to addressing real-world performance, outlier devices, and use patterns by surgeons. Similar to hip replacement, the Kaiser registry, state registries, AJRR, and FORCE-TJR show great promise for addressing these needs, particularly if they are organized as a CRN.

Peripheral Vascular Devices

Peripheral vascular devices are used to treat vascular disease outside the brain and heart. Device categories include peripheral vascular stents, inferior vena cava filters (IVCF), aortic stent grafts, and synthetic surgical grafts.

Carotid Artery Stenosis

Peripheral vascular stents have been widely used in carotid artery stenosis, lower and upper extremity artery stenosis, and visceral vascular disease. A global carotid stent registry was established in 1997[25] and there have been a large number of studies comparing stents and carotid endarterectomy.[26,27] Stenting is now considered an alternative treatment choice to endarterectomy in patients with average to high risk for surgery. Stenting has been shown to be associated with a higher risk of stroke and endarterectomy is associated with a higher risk of myocardial infarction.[28] Research has attempted to identify patient groups that are best candidates for stenting, but no consensus has been reached. The value of stenting versus medical therapy in asymptomatic patients remains unclear. There are number of devices on the market.

Peripheral Artery Disease

With the development of endovascular therapy techniques, use of stenting in peripheral artery disease also continues to evolve, and outcomes are expected to improve.[29] Peripheral artery stenting has not been investigated as thoroughly as coronary stenting, however. Previous studies have shown that drug-eluting stent (DES) therapy reduces the risks of reintervention and amputation with short-term follow-up compared to bare metal stents (BMS) and plain balloon angioplasty.[30,31] The questions of whether DES provide benefits in long-term follow-up and how they perform among different subsets of patients warrant future studies. There are approved devices on the market and many off-label uses.

Aortic Grafts/Stents

Abdominal aortic aneurysm (AAA) can be repaired via open surgery using a synthetic aortic graft, or via endovascular procedure with a stent graft. Over the past two decades, endovascular aneurysm repair (EVAR) has been increasingly adopted as a treatment option. Compared to open repair, EVAR has been shown to be an effective treatment method in selected population.[32] There are at least six major devices on the market with various technological characteristics and modes of failure.

Inferior Vena Cava Filters (IVCF)

IVCF is used in the treatment of venous thromboembolism to prevent pulmonary embolism. It was introduced in 1970s and has gained popularity over the past 20 years.[33,34] However, questions regarding the indication and safety management of IVCF remain unanswered.[35]

A national registry that captures detailed device data and long-term outcomes can help address outlier device performance and enhance the postmarket surveillance in this rapidly growing area of device development characterized by various techniques and grafts. One example is The VQI. The VQI is a national data registry and quality improvement vehicle for the nation's largest group of physicians providing vascular care – the Society for Vascular Surgery (SVS). Since 2002, the VQI has collected data from its members (currently 326 hospitals and practices in 45 states) for outcomes analysis, benchmarking, and quality improvement. These data include more than 120 variables describing the patient's vascular conditions, precise details of the operative procedure and devices utilized during the procedure, as well as detailed perioperative and long-term outcomes. The registry, which has online data collection mechanisms from site of care, is maintained by the Society for Vascular Surgery Patient Safety Organization and is certified as a Patient Safety Organization (http://www.pso.ahrq.gov/psos/overview.htm). There are other integrated delivery system based registries and collaborative efforts including forming CRN can help establish sustainable postmarket surveillance system in the US.

Spinal Fusion

Spinal fusion surgery is an accepted management strategy to relieve pain and neurologic symptoms of lumbar spine degenerative disease.[36] The success of a spinal fusion surgery is associated with selection of an appropriate bone graft or device. Choices include autograft, allograft, bone graph substitutes, and various devices.[37] While autologous bone graft has been the gold standard, other alternatives are being explored due to limitations and morbidity related to autograft.[38] There are currently over 200 different commercial types of bone graft extenders, enhancers, and substitutes.[39] There are also major questions related to non-device and device-based techniques such as cages and spacers.[40]

Although the advantages and disadvantages of cages, grafts, and graft substitutes have been summarized, there is a lack of data comparing spinal fusion surgery outcomes with different types of devices, grafts, or graft substitutes. Despite increasing use of various technologies over the last decade[41-43] there is insufficient evidence to compare cages, allografts, or bone graft enhancers and substitutes. A national registry could help understand the practice patterns and

safety of various technologies is current use. It could establish the standard of care and enable true innovations in spinal fusion surgery.

Cardiac Valves

The first caged ball valve was implanted in 1952; 60 years later, valve replacement surgery can be performed safely with mortality lower than 2% and a low lifetime complication rate.[44] The most commonly replaced valves are the aortic valve and the mitral valve; the most common indication is stenosis. Currently, options for valve replacement include mechanical valves and bioprosthetic valves, performed via several surgical procedures (open surgery, transcatheter valve replacement, or newer options such as robotic surgery).[45]

Results from randomized trials and large observational studies showed no difference in long-term mortality between mechanical valves and bioprosthetic valves in both mitral and aortic positions, but confirmed higher risks of bleeding associated with mechanical valves.[46-48] However, the safety of specific devices is unknown, particularly in various patient populations with different chronic conditions.[49-51] It is still unclear when a mechanical valve or bioprosthetic valve is the ideal choice, or which kinds of valve are associated with best and worst outcomes.

New valve technologies are being invented and surgical procedures are evolving quickly in the current era.[52-54] The growing numbers of devices and procedures require thorough investigation in real-world practice. For example, robotic-assisted mitral valve replacement was found to be as safe as non-robotic surgery, with shorter length of stay.[55] Future study examining long-term follow-up of valve replacement surgery and valve replacement of different positions or multiple valves would help inform our understanding of the safety of new technologies.

Transcatheter valve therapy (TVT) is new technology that was initially introduced to treat severe inoperable aortic stenosis. It is now a fast-growing variety of valve surgery: between 10% and 40% of patients undergoing treatment for severe aortic stenosis are treated with TVT.[56] However, as TVT is adopted, there remain many unanswered questions including patient selection, device performance, quality of life, as well as comparative effectiveness compared with traditional valve replacement. These and other questions remain unresolved due to limited data, limited inclusion of certain patient populations in clinical trials, lack of common definitions, and the rapid arrival of new technologies. The central concern is the “rational dispersion” of this novel technology into US clinical practice,[57] which highlights the need for continuous monitoring. In early 2011 the FDA, in concert with the American College of Cardiology National Cardiovascular Device Registry (ACC/NCDR) and STS Adult Cardiac Surgery Database, other medical societies, industry partners, Centers for Medicare and Medicaid Services (CMS), National Institutes of Health (NIH), and patients started a process that resulted in a National Coverage Decision (NCD). The NCD defined the CMS reimbursement strategy for TVT and enabled the creation of a TVT registry. Since that time, the number of TVT procedures performed in the US and captured in the TVT Registry has increased substantially, and now exceeds 10,000 patients.

Atrial Fibrillation Ablation

Catheter ablation (CA) as an alternative treatment of atrial fibrillation (AF) is a minimally invasive procedure to relieve symptoms and improve quality of life. To understand its efficacy and safety, CA has been compared to traditional antiarrhythmic drug therapy and has been shown to prevent recurrence of AF.[58,59] Whether CA should be recommended as a first-line therapy for selected patients has been debated,[60,61] and there is currently no consensus. The most widely accepted indication for CA is symptomatic AF with antiarrhythmic drug therapy failure.[62]

Although shown to have high success rate (50%-80%), complications following ablation procedures can include tamponade, stroke, pulmonary vein stenosis, or death.[63] New techniques are being developed to improve the safety and efficacy of AF ablation. These techniques include deploying alternative energy sources, ablation strategies other than pulmonary vein isolation, and new ablation tools.[62] Whether or not these innovations offer short- and long-term benefit will be a major area for future research. In addition, because AF is associated with mortality and stroke risk, there are key questions related to the potential of CA to reduce mortality and stroke. The CABANA trial aims to address this question;[64] however, registry-based studies will be necessary to assess these effects in the real world.

ICD/CRT

A CRT-D device is an implantable cardioverter/defibrillator (ICD) enabled with CRT, which is usually indicated in patients with heart failure or ventricular tachyarrhythmia. CRT has been shown to significantly improve outcomes and relieve symptoms among patients with chronic heart failure and/or with ventricular systolic dysfunction.[65-67]

Whether CRT-D is superior to CRT alone has been unclear and warrants further study. A few studies focusing on this topic tended to conclude that CRT-D is superior in some aspects, such as all-cause mortality and cardiac death after 1-year follow up.[68,69] To validate such findings and generalize them to broader populations, a large cohort study with longer follow-up is essential. Furthermore, it is crucial to identify patient populations that would benefit most from such therapy.

CRT is associated with safety issues including implant failure, device malfunction, peri-implantation mechanical complications and/or peri-implantation death. While effectiveness has been an important topic for discussion, it is also critical to have real-world studies investigating the safety of CRT/CRT-D therapy.[66]

ICD has been associated with adverse events including in-hospital complications, postdischarge device- and lead-specific adverse events, infections, thrombosis, and inappropriate shocks. While rates of in-hospital complications with ICD are low, rates of long-term adverse events are uncertain.[70] It was estimated that up to one in five patients receives inappropriate shocks through 1-5 years of follow-up.[70] Riata and Riata ST leads were recalled in 2011 due to insulation failure, which could result in serious adverse events including death.[71] The insulation failure was

detected during postmarket surveillance,[72] indicating the necessity of such research for determining device safety and long-term performance. A device registry with detailed information currently does not exist in the US and is needed to continuously study various ICD/CRT and lead safety and effectiveness.

Cardiac Stents

The first coronary stent was deployed in 1986; by 1999, over 84% of all PCI procedures involved stent placement.[73] PCI has been compared to traditional coronary bypass graft (CABG) surgery for its short- and long-term efficacy.[74-77] While there are concerns that stents have been overused,[78] the newer generation of DES seems to have equivalent outcomes to CABG.[79]

Drug-eluting stents were introduced as an alternative to BMS to reduce restenosis and following reintervention.[80] While the benefits of DES compared with BMS are well known, DES were also associated with late in-stent thrombosis, a rare but fatal complication.[81]

The majority of stents placed currently are DES even though there is still a debate over the magnitude of their advantages over BMS.[82-84] Use of both DES and BMS have proliferated in recent years and there are hundreds of stents on the market. Many second- and third-generation stents are under development or approved for use outside the US; a device registry with detailed information currently does not exist in US and is needed to continuously study various stents' safety and effectiveness.

Laparoscopic and Robotic Surgery

Laparoscopic and robotic technique was first used in surgery in the 1980s[85] and became widely used over the past decade. Minimally invasive surgery (MIS) is now commonly used in abdominal, urologic, gynecologic, ENT, lung, and weight-loss surgery. There have been a large number of studies comparing MIS to traditional open surgeries, or comparing robotic to laparoscopic surgeries. It has been widely recognized that MIS is at least equivalent to traditional open surgery regarding short-term outcomes, and superior in terms of length of stay, blood loss, and perioperative complications.[86-90]

The technology has been adopted rapidly although only a few RCTs have been carried out; observational studies have become the main source of evidence in this field. The evidence on iatrogenic complications associated with less invasive technology requires comprehensive investigation.[91] Such surgery is often performed for cancer where it is important to determine long-term survival and recurrence following MIS surgery.[92] A registry can help understand training requirements for less invasive surgery and outcomes in younger patients.

Ophthalmic Devices

Ophthalmic devices cover a wide range of products including intraocular lenses, lasers, and corneal and retinal implants and stents. The FDA has an ophthalmic devices panel that evaluates effectiveness and safety issues concerning marketed and investigational devices for eye procedures.[93] There are ongoing clinical trials for ophthalmic devices, but real-world data are very limited. A registry could help ensure that these devices are safe in real-world settings.

Surgical Mesh

Mesh has been commonly used across surgical subspecialties to strengthen repairs. These include mesh for vaginal prolapse; for abdominal wall repairs; or for inguinal, femoral, or umbilical hernia repairs. Advantages of mesh use include a lower risk of recurrent failure of the repair. However, a notable risk is that the mesh can become exposed, infected, or associated with chronic pain.[94]

In 2008, FDA released a public health notification of the dangers of the use of mesh for pelvic organ prolapse (POP) that placed it under national scrutiny.[95] In 2011, FDA released an "Update on Safety and Effectiveness for Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse," informing the public of an additional 1,503 events that occurred between January 2008 and December 2010 with POP-type mesh repair.[96] FDA found erosion of the mesh through the vagina to be the most common and consistently-reported complication of transvaginal POP surgeries. Additional frequently reported complications included infection, urinary problems, bleeding, and organ perforation.

In an FDA safety communication regarding surgical mesh for hernia repairs, reported complications included adverse reactions to the mesh, adhesions, and injuries to organs, nerves, or blood vessels. Additional complications associated with hernia repair (with or without mesh) include infection and chronic pain, as well as recurrence of hernia.[97]

Current outcomes data include single surgeon series, short-term trials, or poor meta-analyses. Further, current health outcome studies are subject to the limitations of the population observed or to misclassification of patients due to the lack of appropriate procedure codes.[98] FDA has ordered manufacturers to conduct postmarket surveillance studies on vaginal mesh,[99] but it will take years before data are available. Recent large population-based analyses highlighted higher risk of repeat surgery associated mesh use for POP.[100] This evidence has important implications and is significant from a patient perspective. A national registry is needed to address real-world performance, outlier mesh devices, and use patterns by surgeons.

The Task Force recognizes that the highlighted clinical/device areas vary greatly in terms of the level of stakeholder engagement and degree of efforts to develop a registry. In some instances, there is no US national registry (e.g., spinal devices, but there are several existing institutional, healthcare system-based spinal registries). In other instances, a US national registry has been launched relatively recently (e.g., AJRR) with promising modules of different levels of evidence (from the surveillance level to the patient reported outcomes [PROs]) but there are existing, regional, state and health care registries as well (MARQI, CJRR, Kaiser NJRR) that provide valuable information. In some instances, manufacturers have joined resources to more effectively respond to the FDA mandate (e.g. National Pelvic Floor Disorder Registry), creating a national registry in collaboration with professional societies. Finally, in many other instances (e.g., robotic surgery, ophthalmic devices, AF), there is no existing major registry in the US.

Hence, these areas of opportunity should be interpreted as a recognition of (1) the need for short-term, mid-term, or long-term data in these areas; (2) the existence of a multi-stakeholder consensus that the gap could be reasonably filled via CRNs; and that depending on the registry stage (3) either new efforts (a new registry) should be launched or (4) existing effort should be strengthened (advancing the current registries, linkages, methodologies, etc.).

Chapter Summary Points

1. Registries have particular value when existing electronic data sources, administrative data sources, adverse event reporting, and postmarket studies are likely to be inadequate or uninformative.
2. Priority device areas should be based on the following considerations:
    a) The consequences of device failure are serious for the public health, leading to serious disability or death;
    b) Rapid uptake of the device is expected and adverse events are likely to be rare but very serious;
    c) The device utilizes new technology whose long-term safety and effectiveness are not well understood;
    d) The device has substantial design variations and outlier performance assessment is critical for decision-making;
    e) The performance of the device may vary significantly by surgeons and by important patient subgroups;
    f) The costs of the device are substantially higher than current therapy;
    g) More information is needed to establish best practices for the use of the device, particularly when off-label use is expected and there are substantial legal implications; and/or
    h) Prior regulatory review and reported adverse effects identify unanticipated problems.

Pilot Projects

Pilot Project I.

- Identify a commonly used priority device area where devices have proliferated and there is no national registry.
- Create a consortium of registries that have reasonable device information and good internal and external validity.
- Harmonize the device data information. If required long-term data are not available within registries, consider linkages with claims (including discharge summaries) to obtain informative follow-up data.
- Conduct surveillance and research using distributed analyses if the participating partners cannot combine the data sources.
- Serve as a network for nesting/implementing clinical trials within registries for new device approval.

1. Disease/device focus	Osteoarthritis, other degenerative arthritis, bone fractures. Orthopedic devices
2. Immediate research question(s)	1) Comparative effectiveness of commonly used technologies on attribute (device characteristic) level, 2) Reveal outlier devices (best performing and worst performing), 3) Evaluate surgeon-device interaction based on volumes, regions and specific class of products
3. Stakeholders engaged	Manufacturers, FDA, AHRQ, CMS, Commercial Payers, Professional societies, patient advocacy groups
4. Existing national resources leveraged	State funded registries, Integrated delivery system based registries, Professional Society based registries, Medicare and Commercial claims, PCORI CDRNs, State funded all-payer data sources
5. Efficiencies promoted	National infrastructure creation for large scale investigations rather than isolated underpowered efforts. Data quality improvements and expertise sharing. Centralized data linkages and data purchase costs reduction. Rapid enrollment into clinical studies for new devices
6. Applied national standards & definitions	GMDN standards for device attributes, ICD-9 codes for comorbidities and adverse outcomes events

Pilot Project II.

- Priority device clinical area where device use has proliferated but use is highly variable across specialties and hospitals.
- Enhance existing/emerging national register(ies) by adding detailed device information on a national level and obtain long-term outcome data.
- Compile core minimum data for national and international cohesion and harmonization including using interoperability solutions to extract core minimum data from multiple sources.
- Conduct surveillance and research using the newly enhanced registry.
- Serve as a foundation for starting international collaborations and network for nesting/implementing clinical studies or trials within registry for new device (e.g. AAA, carotid or PAD intervention) approval.

1. Disease/device focus	Vascular disease in a heart, aorta, carotid arteries, or peripheral vasculature. Vascular devices: grafts, balloons, stents, lasers, atherectomy devices
2. Immediate research question(s)	1) Identify core data elements- reduce information heterogeneity in contemporary vascular device evaluation; 2) Comparative effectiveness of commonly used technologies on attribute (device characteristic) level, 3) Evaluate outcomes of off-label and on-label device use, 4) Understand long-term safety of the devices in sub-

	groups, 5) conduct a trial and apply registry and EHR data extraction solutions in prospective pre- or postmarket device setting
3. Stakeholders engaged	Manufacturers, FDA, AHRQ, CMS, Commercial Payers, Professional societies, patient advocacy groups/patients and EHRs manufacturers.
4. Existing national resources leveraged	National registry, Medicare and Commercial claims, PCORI CDRNs, State funded all-payer data source, EHRs,
5. Efficiencies promoted	Infrastructure creation for device surveillance. Centralized data linkages. Rapid enrollment into clinical studies for new devices. For trials- reduce cost, complexity & heterogeneity of case report form and study database design for PAD device studies
6. Applied national standards & definitions	Enhance the data standards for vascular procedures (ARC and similar), create library for vascular devices, ICD-9/10 codes for adverse outcomes events.

Pilot Project III.

- Create a new registry in the single device based (enabled) intervention context where there is no registry to understand the safe application of the technology.
- The device technology did not proliferate and there is one device on the market.
- Short-term results are known but there is variability of outcomes based on individual surgeons and hospitals.

1. Disease/device focus	Thoracic, abdominal or pelvic cancer Robotic device based surgery for cancer excision
2. Immediate research question(s)	1) understanding iatrogenic injury occurrence, specific types of injuries and how they are related to complexity of device use, 2) Impact of procedure volume on outcomes and understanding volume threshold and other factors defining competency in 'real world setting', 3) are there facility factors criteria to ensure safest application of the technology.
3. Stakeholders engaged	Manufacturers, regulators, professional societies, hospitals, and patients
4. Existing national resources leveraged	EHRs, SEER, Medicare, all-payer state registries are helpful but might require new data collection
5. Efficiencies promoted	Centralized learning and multi-specialty application, creating infrastructure and methods for future device applications. Inclusion of future devices in the registry that already exists
6. Applied national standards & definitions	Development of standards for learning and creating definitions for specific injuries that are linked to new technology

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Chapter V. Identification and Optimization of Analytical Methodologies for Device Evaluation

A National System of surveillance of numerous devices will likely be characterized by a CRN that integrates input from several component registries, EHRs, and administrative claims data. Chapter III characterized features of the component registries comprising a CRN. This chapter identifies key data features arising from the integration of information obtained from different sources, describes analytical challenges that may arise due to heterogeneity in data collection, in patient populations and in operator populations and suggests methodological approaches for addressing some of these complications.

Through a thoughtful governance structure (Chapter VI), a CRN will also facilitate structured reuse of data, which in turn will minimize the amount of de novo data needed to be generated to address diverse scientific questions. One key question relates to signal detection – the identification of statistical associations between a medical device and "negative" outcomes heretofore unknown or unconfirmed. Leveraging the CRN for signal detection requires consistent, standardized data that sufficiently specify the medical devices under study and contain the outcomes of interest involved in ongoing assessments of benefit-risk ratios. The validity and utility of findings from signal detection using a CRN rests heavily on developing and implementing scientifically valid analytical protocols that specify the signals of interest, how they will be monitored or assessed (including how accumulating information will be incorporated) and the steps to be followed upon detecting any putative signal (sometimes referred to as a signal escalation process). This approach also sets the stage for far more efficient and robust means to document signal mitigation as newer, improved devices

Analytic attributes of a CRN for signal detection: In general, medical device issues are rare, and safety signals are difficult to identify. Differences in patient outcomes based on procedure or medical device use are largely driven by procedure indications, patient selection and risk and other factors such as operator training and proficiency. Meaningful medical device surveillance requires robust data analytics and processes for evaluating data in order to determine whether there may be a safety signal. There is no single or accepted method for signal detection although several approaches and settings where they are best suited are described later in this chapter. Registry programs described in Chapter III provide different approaches for signal detection: direct review of clinician reports of unexpected problems with devices in the VA CART Program; assessments of aspects of device safety in clinical practice as part of post-approval studies in the TVT Registry; and robust statistical modeling to detect meaningful outcomes differences based on medical device use as is illustrated with the DELTA program.[1] All these approaches have strengths and weaknesses, and the methods for analysis and determination of potential safety issues will continue to evolve. However, meaningful device surveillance requires sound analytic approaches and evaluations of device safety data. Given the unique aspects of device monitoring and regulatory considerations, this should be a firm prerequisite for a CRN. The analytic portfolio of the CRN should not only include expertise in recognizing and handling data heterogeneity, but also for prospectively leveraging such heterogeneity to make better inferences.

emerge.

Similarly, a CRN will enable shifting some premarket device data collection requirements to the postmarket setting. Such a shift requires the CRN to use valid and reliable data elements that reflect the outcomes of interest in well-defined populations. A highly functioning CRN could also provide important long-term device performance information for mature devices, solid intelligence to help improve the device as well as evidence on which patients are the best candidates for a device.

Data Heterogeneity and Implications for Knowledge Generation

By its very construction, a CRN will house data with specific features that will differ across subsets of the data. Examples include variability in measurement error associated with specific data elements, differences in populations implanted with a particular medical device, representativeness of the sample populations in component registries, differential skill and experience of the implanter/operator of the device, variation in data completeness rates and differences in device effectiveness across subpopulations. Some data heterogeneity is unwelcome, such as measurement error, and steps should be taken minimize such effects. Other data heterogeneity is welcome, and methodology that exploits it should be utilized. Patient heterogeneity among device recipients falls into this category; such heterogeneity can be leveraged to learn about device safety and effectiveness in specific subgroups. Statistically valid use of information in a CRN therefore requires both acknowledging and handling data heterogeneity.

Target versus Included Patient Population, Site and Physician Types

With procedure-based or device-based registries, information is typically assembled on all patients implanted with the device, regardless of whether the device is implanted for approved or off-label indications. Consequently, within a CRN the sampling frame is likely to vary according to practice patterns associated with the component registry – including variation in site effects (e.g., specialty center, tertiary hospital) and variation in operator or physician effects (e.g., fixed effects such as specialty, physician experience and operator-specific effects). For instance, in some practices, cardiac surgeons may constitute the majority of device operators whereas in others cardiac interventionalists may comprise the majority. Differences in the types of physicians using the device can be exploited to explain variation in the success of device deployment or other measures of device performance, and to explain differences in clinical outcomes. Approaches to account for physician or site heterogeneity in assessing device and clinical outcomes will involve separation of random and deterministic components through the use of fixed or random effects within statistical models. While such approaches exist in the statistical literature, their use in regulatory settings has been limited. The Task Force recommends evaluating approaches that would account for multiple sources of heterogeneity within a CRN for device assessment.

Differences in characteristics of included populations, such as on- and off-label populations, strengthen the ability to learn about device safety and effectiveness in the postmarket setting

through a broadening of the design space. Variability in measurable characteristics of patients exposed to the device increases the statistical power to estimate differences in device effectiveness. In this sense, population heterogeneity in a CRN constitutes a potential advantage that should be fully exploited.

Variable Definitions and Data Collection Strategies

While registries are typically accompanied by detailed variable definitions and data collection protocols, measurement errors associated with particular data elements will inevitably vary. Information assembled within a CRN will thus be characterized by such differences. For instance, consider information within the CRN composed of both patient self-report, such as "patient experienced chest pain prior to hospital arrival," and billing claims information, such as an ICD-9-CM code of 412 (old acute myocardial infarction). The measurement error associated with the self-report differs from that associated with the billing data. Even among *like* data elements, measurement error could vary systematically: older patients are less likely to report chest pain than younger patients, and hospital billing practices vary across and within teaching and non-teaching hospitals. Choice of billing codes may differ across hospital systems, and certain fields in EHRs may use alternative phrases across implementations that result in imperfect matching when aggregating data across multiple sources within the CRN. Finally, with new data acquisition technologies, imaging information (having different resolutions) and other high-dimensional data summaries are likely to populate registries. These observations highlight the foundational principles of measurement (Panel 2). The validity of statements about device safety and effectiveness rests upon adhering to measurement principles. When the principles are violated, approaches to address the shortfalls are required. These may range from eliminating variables from some analyses to drawing additional samples to characterize the reliability of measurement for use in subsequent inferential procedures. Strategies to standardize variable definitions and collection processes may originate at the level of the participating registries and related entities or at the level of the CRN, depending on the structure of the CRN and the maturity of the participating registries. Heterogeneity thus may potentially be addressed both through the infrastructure composing the CRN itself and in the methodological approaches applied to analysis of data emerging from the CRN.

Panel 2. Measurement Principles

1. Measurement captures the theoretical construct of interest
2. Measurement is stable over time and across cases
3. Measurement error is random (not systematic)

Variation in Data Completeness

Heterogeneity in data completeness is likely to arise in a CRN for a variety of reasons. Subjects exposed to a device may be missing entirely from a component registry or specific data elements may be missing for a subset of the sample. The mechanism by which subjects or data elements are missing influences the analytical approach adopted. For instance, information on an adverse event may be missing (1) completely at random, meaning that the probability of

missingness is unrelated to site, physician or patient observable characteristics; (2) at random, meaning that the missingness mechanism is related to only recorded characteristics; or (3) not at random, meaning that subjects experiencing the adverse event are less likely to have adverse event information recorded than those not experiencing an adverse event. Furthermore, this missingness mechanism has implications regarding what type of information sufficiently describes device performance within component registries. For example, if missingness is not at random, conclusions obtained using summary statistics via a distributed network approach will be biased. It is essential to have a clear understanding of the conditions in which component registry summary statistics provide unbiased estimates of device performance and when such summaries are biased.

When missingness cannot be differentiated from *not applicable* or *not present,* additional issues arise. For instance, the absence of a recorded history of heart disease in an electronic record could be interpreted to mean (1) the patient had no history of heart disease or (2) the information was not solicited and so it is missing. While valid approaches to dealing with non-response are widely available,[2] the complicating issues with missing information in a CRN are challenging because the data are dynamic and high-dimensional: information is growing over time, there are different measurement errors associated with different data elements, the number of data elements is large and there are unmeasured selection factors influencing who gets which device (i.e., lack of randomization). Furthermore, unlike in the closed population of a standard randomized trial, the size of the population for which no data is available may be unknown. Sales figures are occasionally proposed to measure the total population of devices in use, yet this approach suffers from the inherent lag between purchasing and initial use for many types of devices (which can be substantial). Standard approaches to missing data, such as multiple imputation methods, require the creation of multiple "completed" datasets by making use of all observed information. The dimensionality of the imputation problem will be large. The Task Force recommends requiring guiding principles and proof of concept illustrations for handling missing data in CRNs where data dimension could be large.

Assessing/Refining the Risks and Benefits

The availability of a CRN assembled across a broad array of patient and operator populations provides a unique opportunity to inform both device premarket assessments and postmarket labeling extensions—e.g. to facilitate such decisions over the TPLC. TPLC opportunities rest on the observation that combining available information may reduce uncertainty about device safety and effectiveness or benefit/risk in a particular subgroup compared to the safety and effectiveness or benefit/risk of the device in existing populations. The statistical notion underpinning this idea relates to poolability: to what extent can information be borrowed across subpopulations to inform questions in a particular subpopulation.[3]

The Task Force identifies two prototypical pooling situations: (1) labeling extensions: pooling data across heterogeneous patient populations implanted with a particular device to learn about benefits/risks in a new patient population; (2) clearance for competitive iterations of

similar devices: pooling data across multiple devices within a particular patient group to infer the benefits/risks for a new but similar device.

Opportunities for label extensions using data drawn from the CRN require assumptions about the level at which the available information is poolable and about the required minimum number of patients observed in the new subgroup or indication. For instance, assume the number of patients having the new indication is small (Box A in Figure 4) relative to the number of patients exposed to the device who have the approved indications (Box B in Figure 4). At one extreme, device performance for the new indication could be assessed by using outcome information only from the new group. In this setting, there is no pooling of information (Box A) among on-label and off-label populations. At the other extreme, device performance for the new indication could be assessed using data from all patients in the CRN. In this situation, there is complete pooling of information (Box C). The former extreme assumes nothing can be learned about device exposure in the new indication group from outcomes for patients with approved indications; the latter extreme assumes that device performance in the new group is virtually the same as performance in the approved indication group. Both assumptions are unrealistic. The compromise pools outcomes by weighting the average outcomes for the new indication group (Box A) and the average outcomes from the approved-indication group (Box B). This compromised estimator has smaller error (and hence more efficiency) than restricting conclusions to patients falling into the new indication alone. It also mitigates potential bias arising from incorrect choices of either full pooling or no pooling in situations where these actions are not optimal.

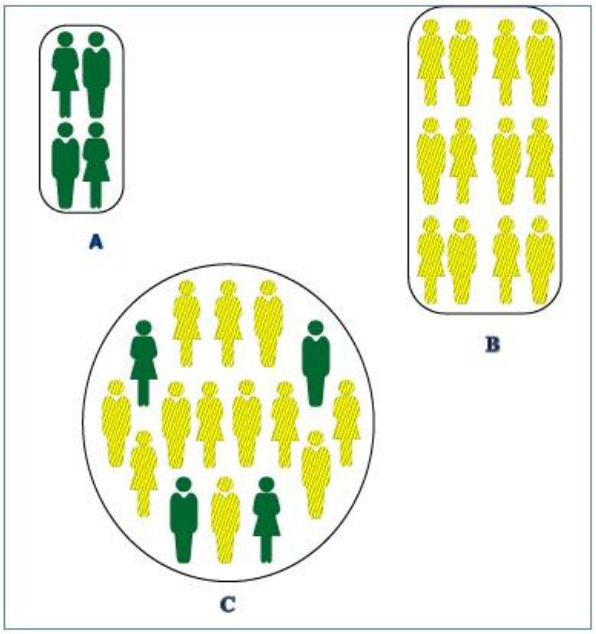

Figure 4.

A similar strategy could be adopted for producing evidence to inform clearance decisions. For instance, when considering drug-eluting stents, groups (Boxes A and B) could be formed by specific manufacturer, by specific manufacturer-version or by a finer classification. The assumption to be defended is that information about safety and effectiveness for a new, similar device is informed by safety and effectiveness for all similar devices. Such an approach relies on contemporary data and, in that regard, has stronger face and statistical validity than approaches using OPC based on historical data.

Either use of the data in the CRN requires some pooling of information. The Task Force recommends developing essential and general principles for CRN constructs related in particular

to label extensions of approved devices and pivotal clearance of new device iterations, e.g. to work in more mature device pipelines. Such principles should be grounded in empirical studies and provide recommendations on the validity of pooling assumptions, coherence of device comparisons, determination of a minimum number of observations or minimum number of events in the group of interest required and approaches to representing uncertainty of the strengths of relationships through probability distributions. These principles will likely have much in common with related concepts discussed in the recent FDA draft guidance on leveraging existing clinical data for extrapolation to pediatric uses of medical devices.[4]

Beyond Traditional Risk Modeling: Patient, Industry, and Regulator-Based Utilities

Traditional risk models, adjusting for patient risk and frailty, determine the probability of procedural outcomes, most commonly death or other post-procedural complications such as stroke, infection or renal failure. While there is clear value in determining these risks on a short-term basis, it is essential to be able to follow and predict outcomes years after device exposure. This type of statistical model development should be an integral part of CRNs. Moreover, because risk models are based on patient data collected over a period of time, as new developments are made and the patient population changes, models must be periodically updated to reflect current data. Accordingly, model development should be regarded as an ongoing process that requires continuous analysis of incoming data to the CRN, a critical feature of the Task Force emphasis on the sustained activity of CRN structures.

The safety of a procedure is only part of the decision-making process as to whether to recommend it. Patient benefit must be considered as well; because the procedure can be performed safely does not mean it should be done. If it affords the patient only minimal benefit, then the patient has received poor treatment. Patient reported outcomes (PRO) and patient reported health status determined from a variety of published scoring protocols can provide an objective measure of patient benefit. The patient reported data provide information for developing statistical models that predict the probability of PRO scores. The Task Force suggests that results of these models could serve as a meaningful measure of predicted patient benefit. Statistical benefit/risk models should be developed to predict both the probability of procedural mortality, major non-fatal complications, and the probability of clinically meaningful patient benefit.

Similarly, assessments of the risks and benefits of medical devices require trade-offs that are weighted by preferences or, more generally, utilities. A CRN that links information on stakeholder preferences presents a new opportunity to summarize quantitatively the benefit/risk trade-off. For example (see Maestro Rechargeable System text box), the FDA approval of the

Maestro Rechargeable System: A weight reduction survey was administered to provide information for a text box in the product label that has a description of the risk-benefit information used in assessing the neuro-regulator.

Maestro Rechargeable System, a subcutaneously implanted rechargeable neuroregulator to treat obesity, incorporated patient preferences obtained via a discrete-choice experiment.[5]

Obtaining utilities involves numerous design and sample selection issues, and the generalizability of empirical estimates across different devices, different patient populations and different practice regions are unknown. Nonetheless, the Task Force recognizes that creating stakeholder utility banks and subsequently using utilities from the banks to assess post-approval device safety and effectiveness provides a valuable input to assessing the benefit/risk of medical devices. Utilities could be folded into signal detection algorithms as well as used to explain heterogeneity in device and clinical outcomes.

Other Analytical Issues Associated with Benefit/Risk Assessments within a CRN

With its multiple data sources, a CRN has great potential to aid in post-approval prediction and extrapolation of safety and effectiveness outcomes. Expected outcomes in specific groups, defined by patient, device or operator characteristics, can be computed to bolster inferences when premarket data are sparse and to inform on postmarket device performance. A particularly important patient subgroup is the pediatric population. A better understanding of how data observed in adult populations can be utilized to infer device performance in pediatric populations and deserves careful assessment. CRNs, covering broad populations and including information from multiple data sources will be well-positioned to inform such assessment.

Safety Signal Detection in the Context of a CRN

Safety signal detection for medical devices using CRNs is a concept that is broadly appreciated but imperfectly understood. Many different types of signals are of potential interest to the various stakeholders, and the CRN will require a clear understanding of the ultimate goal. Signal detection methods fall into four broad groups (Table 7): (1) separation, (2) heterogeneity, (3) exclusion and (4) deviation.

Table 7. A Taxonomy for Signal Detection

Type	Purpose	Example
Separation	Identify divergence between two devices	Is the adverse event rate following drug eluting stenting different from that following bare metal stenting?
Heterogeneity	Determine if and when one process differs from a collection of processes	If and when does the average post-implant infection rate for Surgeon A differ from the average infection rate for all surgeons in the country?
Exclusion	Determine when a signal is sufficiently refined that a threshold value may be excluded, even if the process is relatively constant	When does the average hospital mortality following implantation of a left ventricular assist device in Hospital A exceed 15%?
Deviation	Determine if and when a single process leaves a pre-defined area of acceptability	If and when does the incidence of inappropriate shocks by implantable cardioverter/defibrillators leads exceed x?

Separation

This setting involves examination of two processes over time with a primary goal of identifying separation or divergence between the processes (focus on relative differences) rather than to determine the absolute level of either process. For instance, Resnic et al. considered separation of adverse event rates when comparing a drug-eluting stent and a bare-metal stent.[6] A signal was determined to be detected once the cumulative rates were assessed to be sufficiently far apart. Hauser and colleagues examined separation in the simulated analysis of two separate models of implantable cardioverter/ defibrillator leads.[7] A signal was declared when a log rank test determined that two survival curves had significant separation from one another. In the Hauser example, the focus was on how soon a difference between the two curves could be detected, not on the absolute values of the survival curves. Both articles used a propensity scoring approach to achieve comparability between the groups at baseline.

Automated medical safety surveillance: The Data Extraction and Longitudinal Trend Analysis approach (the DELTA network) potentially offers real-time early monitoring for medical device safety surveillance. The DELTA methodology has been successfully applied retrospectively with data from a high volume three-hospital coalition. It demonstrated the feasibility of an early warning detection system for faulty Fidelis ICD leads.[8] The DELTA network was utilized in a prospective propensity-matched cohort analysis of 7 newly-introduced cardiovascular devices, using clinical data captured in the Massachusetts PCI database from 2003 to 2007. For this project, the NCDR CathPCI registry was used as the data collection tool. The DELTA system identified issues in 3 out of 21 safety analyses that triggered sustained alerts in 2 implantable devices. Patients receiving a Taxus Express2 drug-eluting stent experienced a 1.28-fold increased risk of post procedural myocardial infarction (2.87% vs 2.25% for those receiving alternative drug-eluting stents). The authors determined that automated prospective surveillance of clinical registries is feasible and can identify low-frequency safety signals for new cardiovascular devices.[6] Presently ongoing in a DELTA network study is a unique prospective surveillance study based on analysis of ACC-NCDR data elements at a network of independent medical centers in Eastern Massachusetts.

Separation is an appropriate signal for which to screen assuming data can be accessed repeatedly over time as information accumulates. While both of the prior examples looked for separation retrospectively, establishing a prospective screening process to detect separation between two processes also works in principle. A sustainable CRN structure would facilitate such applications. A screening process within a CRN could be automated, relying on continuous updating of the statistical models to adjust for confounding among patients exposed to different devices as new data became available. Data requirements to detect separation are high in order to account sufficiently for important baseline risk differences between patients exposed to different devices, including additional information to account for time-based differences if the devices compared are not utilized contemporaneously. Derivatives of separation applied through a CRN could also promote a real time approach to

reassurance that new devices touting design modifications successfully eliminate the cause of any previously detected safety signals observed in the predicate devices.

Heterogeneity

The primary objective of screening for heterogeneity involves determination of when or if one process differs from a collection of other processes. Sherlaw-Johnson and colleagues examined patients undergoing either coronary bypass grafting or valve surgery, focusing on differential infection rates across surgeons.[9] Heterogeneity is also regularly employed at a single point in time, rather than across time, using a variety of approaches: the empirical Bayes gamma Poisson shrinker,[10] proportional reporting ratio,[11] Bayesian confidence propagation neural network[12] and general Bayesian hierarchical modeling.[13] The Task Force recommends that a CRN should deploy these tools in the context of a pre-specified analysis plan. Such a plan would sharpen the focus of efforts appropriately and clarify differences between findings that should be viewed as hypothesis-generating versus hypothesis-testing (or, in the absence of an analysis plan, hypothesis-free). The analytical plan will drive the selection of methods as well as the steps to be taken if heterogeneity is detected. Depending on the outcome and population variables being considered, the impact of detected heterogeneity could range from directly actionable to primarily descriptive.

By its very nature, heterogeneity is an approach that requires more information than that needed to assess the performance of a single device in a single homogeneous population. This is true both in terms of the amount of observation within a given sampling unit (which enables the fragmentation of a previously homogeneous population) and in terms of the number of sampling units collected (so that there is sufficient power to detect different subgroup effects). The Task Force recognizes that one aspect of heterogeneity that may be of particular interest is that associated with the learning curve of operators using or implanting multiple devices over time. Furthermore, the degree to which CRN structure can optimize the elimination of heterogeneity in data quality, measurement error and definitions, e.g. eliminate barriers to poolability, concomitantly positions the enhancement of methodological opportunities to enrich safety and benefit/risk information emerging from real world heterogeneity associated with device identifiers, operator skills and patient subgroups.

Exclusion

This type of detection is of interest when a process is stable over time but there is interest in determining when the precision in the estimate about the process becomes tight enough to rule out a threshold value, such as zero for a rate difference estimate or one for a hazard ratio estimate. Applications that consider exclusion over time are not common in the literature. Exceptions include Celli and colleagues,[14] who considered the evolution of the hazard ratio over time comparing active treatment versus placebo for patients with chronic obstructive pulmonary disease, and Poloniecki and colleagues,[15] who examined average mortality for transplants in one hospital compared with a fixed limit. CRN data requirements for screening for exclusion include information to monitor the separate processes and ensuring a comparable baseline for the two processes.

Deviation

The primary goal of screening for deviation involves the detection of the time at which a process departs from a region of acceptability to a different region which might then warrant action. Statistical process control methods[16] are frequently employed to monitor possible deviations over time as well as cumulative sum charting against a fixed threshold.[17] Duggirala and co-authors applied the multi-item gamma Poisson shrinker to perform a retrospective analysis of implantable cardioverter/defibrillator leads over time, declaring a signal when excess values were observed.[18]

CRNs can provide a basis for deviation assessments. Provided that the relevant classifying variables are readily available and the pertinent groups are of sufficient size to obtain the necessary precision, screening for deviation might be applied to detect important shifts in performance by lots or batches of devices. Screening of this type might be warranted if certain changes were made in the manufacturing process or if a supplier of parts for the device changed. Deviation screening could even be used effectively to monitor the performance of a single device for which performance boundaries were available to serve as thresholds. Such an approach is attractive for first-in-class devices for which no natural comparators are available, or as an additional check on a device for which comparative assessments were also being performed. Implementation of UDI would greatly facilitate such an approach to deviation assessments by CRNs.

Selecting a Threshold

Regulators and other stakeholders will need to agree upon a threshold that determines if a signal is present. The tradeoff between sensitivity and specificity related to choice of threshold becomes progressively problematic as increases are made in the number of both signal detection procedures at a fixed point in time and times at which such procedures are performed. Especially troublesome is the situation where there is no natural stopping time for the signal detection process. While it is possible to control an overall family-wise error rate in a frequentist setting by splitting the total error rate into the pieces of an infinite convergent series,[19] this approach is better suited for controlling across tests at a finite number of time points than for controlling a testing process expected to last an unknown number of years. Another approach for setting thresholds involves determining the threshold based on available resources within a fixed time period. Using information in the CRN, simulation techniques could be used to quantify the behavior of the various signal detection screens to be employed using reasonable assumptions, and select those values of thresholds that correspond to identifying the *k* strongest signals. Here *k* would represent the number of signals for which resources were available for a given period of time. This could be useful in a relative setting, but would not necessarily be optimal for discriminating between a scenario where the important signals numbered less than *k* and a scenario where the important signals numbered more than *k.* Understanding variation in perception of reasonable thresholds across stakeholders and across specific device areas will be critical to informing appropriately applied statistical methodologies.

Enhanced opportunities for stakeholder engagement through novel avenues within CRN structure (Chapter 6) can be strongly leveraged to optimize threshold definition(s).

Prospective postmarket safety surveillance will offer significant advantages over retrospective safety analyses. The results would be both hypothesis-generating, requiring further validation related to determining hazards of a particular medical device, and concomitantly provide a landscape for more efficient documentation of elimination of those hazards by new, better device design or other mitigation steps.

Conclusion

CRNs are well-positioned to inform premarket study designs and postmarket performance, and hence positively impact the total product lifecycle for related devices. The Task Force emphasizes that there are multiple data-related features of CRNs that require attention in their development and structure. This chapter highlighted some of these features. Other aspects of the creation of CRNs also merit investigation. These relate to novel methodologies for linking information among vastly different data sources, the development of better electronic capture methodologies[20] including mobile applications (see MedWatcher text box), validation of data fields obtained from different sources, (e.g., use of administrative claims data to obtain follow-up information,[21] and big data environments). High Performance Integrated Virtual Environment (HIVE) is a distributed cloud-based environment which is developed by FDA and George Washington University (GWU) supported by a team of 30 bioinformaticians, scientists, software developers and epidemiologists. HIVE was first implemented at FDA's Center for Biologics to optimize the storage and analysis of extra-large Next-Generation Sequencing data. Presently, FDA HIVE (mini–HIVE) is housed at HPC-CDRH and it is being implemented around the Agency for various applications involving big data deposition, retrieval, annotation and computation.[22] There are four major sectors of HIVE: (1) research and development (R&D) HIVE at GWU is designed to handle pilot projects and small to medium size production projects; (2) mini-HIVE hosted at FDA is targeted as a development and research production platform for implementing new cutting edge tools and conducting research by regulatory and research scientists; (3) colonial one HIVE GWU at the Ashburn datacenter is targeted for large-scale projects and massive computational tasks across varied datasets and (4) maxi-HIVE is FDA's regulatory computational platform designed to host and to perform high performance massively parallel computations. Public HIVE (deployed at GWU) further propagates developments of HIVE capabilities to a wider scientific community and can support seamless integration of big data analytics supported by FDA and other stakeholders.[23]

HIVE has authorization to operate within regulatory environment and to review big data in high performance computing environments. HIVE has also been recognized to be compliant with FISMA moderate categorization schema. HIVE's hexagonal security layers include institutional firewall, high performance computing environment access accounting, HIVE-encrypted identity management, PIV card authentication, honeycomb hierarchical security model and delocalized data flow. In addition, it provides a possibility to configure the system and achieve hardware/software segregation where regulatory review systems can be physically separated

from non-regulatory applications. This could constitute one lessons learned model for CRNs intending to deliver customized information from central data architecture to multiple individual stakeholders.

Use of non-conventional (clinical and non-clinical) data sources and tools is expected to offer a great opportunity for the development of new evidence synthesis methodologies addressing the need for more individualized risk/benefit assessment and more predictive analysis of product performance. HIVE-CBER/CDRH team is currently conducting regulatory research on arthroplasty-related outcomes using orthopedic registry data and adapting new analytical tools for epidemiological data analysis (e.g., clustering, classification and heat map generation). The HIVE-based data integration platform and analytic tools will serve as a basis for development of novel methodologies for systematic evaluation and synthesis of all available evidence that is necessary for a comprehensive and up-to-date risk/benefit balance determination at any point of the product life cycle.

MedWatcher: A mobile application that lets people search the newly accessible FDA database of side effects for drugs and medical devices. Patients can also report their own experiences through the app, which are relayed to the Agency.

While the success of CRNs will depend on many factors, data quality and richness and analytical approaches are key factors. The recent white paper released by the Planning Board[24] proposed a tiered data infrastructure: Tier I includes the minimal amount of information needed to perform surveillance on individual products; Tier II includes information facilitating more comparative or nuanced analytical approaches; Tier III enriches information qualitatively beyond that in Tier II. A National Medical Device Evaluation System structured around CRNs can facilitate the incorporation of multiple sources of information, some of which may be incomplete, while still capitalizing on the data they provide. The CRN might conceivably draw from multiple populations through data from different hospital systems, as well as assimilate multiple outcomes from distinct or overlapping data repositories such as the national death index, regional cancer registries, or claims data from multiple payers. The Task Force envisions the mixture of a growing repository of historical information with prospective data collection that includes both updates on existing sources and new information from new randomized trials, randomized registries or various hybrid designs.[25] Further methodological developments will be needed to determine how to continuously and optimally leverage these disparate data sources.

Chapter Summary Points

1. A CRN will inevitably involve heterogeneity in data collection, patient populations, clinical centers and operators.
2. Information aggregated to the component registry level (e.g., distributed summaries) may be sufficient for some medical device performance activities, such as signal detection, but may be insufficient for other activities, such as benefit/risk determinations.

3. Key aspects of CRN construction include attention to minimizing quality heterogeneity (data element definitions, measurement error, etc.), supporting poolability to maximize information opportunities from enriched patient, device and operator heterogeneity.
4. By capitalizing on the variation across the CRN through novel methodology, quantitative metrics of the benefits/risks can be constructed for particular patient subgroups or for particular devices.
5. Leveraging the CRN for signal detection requires consistent, standardized data that sufficiently specify the medical devices under study and that contain the outcomes of interest.
6. Statistical models can summarize information in registries vital for premarket study designs, hence positively impacting the total product life cycle for related devices.

Pilot Projects

Pilot I

Determining the Sufficiency of Summary Statistics for Use in CRNs

Methodology-focused pilot project: theoretical derivations, simulation-based summaries, and illustration of approaches to characterizing conditions in (in the context of a CRN) which:

- Component registry summary statistics provide unbiased estimates of device performance
- Summary statistics are biased
- Missing data

1. Disease/device focus	Applicable to any condition or device
2. Immediate research question(s)	When do component registry summary statistics provide unbiased estimates of device performance? When are registry summary statistics biased and can approaches reduce the bias?
3. Stakeholders engaged	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. Existing national resources leveraged	Methodology illustrated using existing national or international registries such as ICOR, TVT Registry, etc.
5. Efficiencies promoted	Study results will indicate when it is statistically valid to use a "distributed" network approach versus combining individual participant data. Consequently, results from this pilot will promote the best (optimal) use of patient data and thereby reduce the number of observations (patients) required to inform regulators, patients, and physicians.

Pilot II

Pooling Data for Making Regulatory Decisions in CRN

Methodology-specific pilot: theoretical derivations, simulation-based summaries, and empirical approaches to characterizing the validity of pooling assumptions and the coherence of comparisons, determination of a minimum number of observations required, and approaches to representing uncertainty of the strengths of relationships in the context of label extensions, signal detection,, and clearance of predicate devices.

1. Disease/device focus	Applicable to any condition or device
2. Immediate research question(s)	What is the validity of pooling assumptions made in the context of CRNs? What types of devices and populations can be compared? What is the minimum number of observations required for label extensions or clearance of predicate devices? How can uncertainty of the strengths of relationships be best represented? How can big data techniques (e.g., data mining, machine learning) be utilized for signal detection?
3. Stakeholders engaged	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. Existing national resources leveraged	Methodology illustrated using existing national or international registries such as ICOR, TVT Registry etc.
5. Efficiencies promoted	Study results will indicate how to develop more efficient (statistical efficiencies) estimates for regulatory inferences.

Pilot III

Statistical Approaches for Informing the Device Total Product Life Cycle

Because the CRN will enable shifting some premarket device data collection requirements to the postmarket setting, this shift requires the use of valid and reliable data elements that reflect the outcomes of interest in well-defined populations. Approaches for using CRN data to provide: (a) important long-term device performance information for mature devices; (b) solid intelligence to help improve the device; and (c) evidence on which patients are the best candidates for a device require assessment and illustration

1. Disease/device focus	Applicable to any condition or device
2. Immediate research question(s)	How comparable are data elements and definitions between claims data and pivotal clinical trials? Case Study: percutaneous mitral valve devices will be used to assess validity of outcomes event ascertainment (death, re-hospitalization, heart failure progression, stroke, etc.) using claims data compared to classical clinical trial processes. Can patient reported outcomes be utilized to assess device benefit? How can stakeholder preferences be factored into the benefit/risk assessment?
3. Stakeholders engaged	Statistical and epidemiological researchers from industry, academia, and FDA; for illustrative application, patient representatives from example device area and CRN component registry owner representatives.
4. Existing national resources leveraged	Methodology illustrated using existing national registries such as the MDEpiNet PASSION programs, the ACC-NCDR TVT registry; ONC/CDISC definition dictionaries; ICD code structures. Stakeholder utility banks could be constructed and leveraged for future device assessments.

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Chapter VI. Perception, Ethical, and Related Considerations

Keys to CRN Sustainability

The functionality, impact and sustainability of the CRNs, and indeed of the National Medical Device Evaluation System overall, will be affected by the quality of the relationships among the component registries and their alignment with stakeholder values in general (text box). These relationships will be shaped by the actions of the CRNs via their governing bodies and the perceptions and participation of stakeholders, as well as external policies and events. While operating within and thus aligned with the National System and its governance structure, the spectrum of CRNs will require a high degree of independent governance. To assure that CRNs will be sustainable, the governing bodies must take responsibility for delivering sufficient value to all stakeholders so that they continue their participation in and support of the CRN efforts. This chapter focuses on considerations relevant to CRN governance in the delivery of an appropriate product, value and price for all stakeholders. Such a product requires a governing body that enacts policies relating to patients, publications, intellectual property, data quality and other topics of importance to stakeholders that are simultaneously consistent with those of the governing body of the national medical device system. Additionally, the governing body of a CRN should deliver and price its product such that stakeholders agree it yields good value for the price and is

Collecting data once, serving multiple purposes and stakeholders. The inclusion of multiple stakeholders collaborating to define multiple short- and long-term purposes is a more broad-based strategy that has the potential to provide more long-term sustainable value than could be achieved if attempting to only meet the specific needs of one stakeholder group. As an example, a registry could apply and be approved to report quality measures to CMS while supporting evidence for payer reimbursement and using the data as a condition for device approval. In this case, the principle of collecting data once to populate multiple downstream data sources would lead to a more comprehensive evaluation of device performance and inform decision making across multiple groups including patients, providers, industry, payers, and regulatory authorities. This type of dual- and even multi-purposing is central to the Coordinated Registries Network (CRN) approach.

The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) is national registry who development, implementation, maintenance and output are funded by the Swedish government as a national health care resource. Participation by all operators and cath labs in the country is mandatory. Operations are third party contracted by the Swedish government to university-based experts. Integrated into the national health system with unique patient identifiers, outcomes for all patients in all procedures can be subjected to retrospective analysis, anreports comparing outcomes with various brands of bare metal and drug eluting stents, as well as across the two device classes, have been reported. The national infrastructure has also been utilized to greatly reduce cost and speed enrollment in a prospective randomized trial of aspiration catheters used for ST-elevation MI.[1-3]

more attractive than other options that are or may become available.

Sustainability considerations for traditional registries and thus for CRN structures must include financial awareness. Current traditional national registry operating budgets range from approximately $5MM to $40MM per year. These budget numbers do not reflect the workload and in-kind contribution of health care institution employees who must learn the intricacies of varied registries and perform data entry tasks at the site level. Unlike nations such as Sweden, Israel and Japan, it is highly unlikely that the US federal government will fund a centralized American solution (see text box). In the United States the government is in a position to require registry participation for reimbursement through Coverage with Evidence Development (CED) from CMS, historically providing a strong role in launching multiple device registries (e.g., ICD, INTERMACS, TVT registries). However CEDs are not intended to be long-term solutions, and if the registries they promote do not provide independent value, termination of the CED requirement may be accompanied by termination of participation in the registry.

Central to the emphasis of this chapter is the recognition that whether stakeholders contribute dollars, expertise, personal exposure, health information or combinations thereof, governance entities must ensure that any single CRN produces unique, "priceless" deliverables that address specific stakeholders' constituencies. With such a product, valuable to providers, payers and patients as well as regulators and industry, reasonable financial and other support will be forthcoming. Failing this, no grant or sponsor combination will sustainably support even the most basic operational costs. Operational costs, however, cannot be overlooked. A key questions survey applicable to both CRNs and participating component registries is proposed in Panel 3 below.

Panel 3. Key Cost Question Survey

The responses to a set of key questions will ensure sustainability and provide guidance and infrastructure support for moving from a single, proprietary, closed registry model to one that is multi-pronged and requires collaboration among multiple organizations and funding sources in order to achieve long-term success on a national scale. These questions could be applied either to the participating component registries or to any CRN.

Cost Considerations

26. What organization(s) should fund a registry?
27. What is the strategy for maintaining the registry?
28. What efforts have been made to reduce costs by adopting data standards that are part of the national health IT infrastructure?
29. How will the registry integrate with existing clinical workflows?
30. What efforts have been made to include professional organizations as part of the registry design to reduce the cost of data entry and improve data quality?
31. What open-system architectures can be adopted to permit sharing infrastructure costs and innovation?

Spreading Financial Burden

32. What efforts have been made to work with payers to include incentives for registry participation as a way of reducing costs? For example, linking to quality incentive programs, linking to coverage determination decisions or linking to physician and hospital reporting requirements to CMS or other organizations.

33. What methods are being used to encourage provider participation (incentives, pay for performance, mandates)?
34. How can data access and transparency be improved to provide value to manufacturers and regulators, resulting in reduced cost and time and improved analysis to inform regulatory approval decisions?

Increasing Long-Term Value

1. What provisions are being made to align with data standards efforts such as MDEpiNet, PCORnet, Sentinel, HL7, etc. to enable linkage to other data sources?
2. How is the public (including patients, providers) informed about data availability?
3. What methods can be used engage the public to use registry data?
4. Has the registry provided data to monitor for appropriateness and "indication creep" over time?
5. Has the registry provided users with actionable information that enhances quality of care?

Governance Models

The MDRTF recommendation for CRNs brings with it the important need for novel governance models. As entities envisioned within a National Medical Device Evaluation System, CRNs would presumably operate within the larger governance model of the National System itself. To achieve and sustain their missions across the broad spectrum of medical devices, however, CRN governance would clearly require a substantial degree of independence from the National System as well. Furthermore, as CRNs strategically employ multiple component registries, each of which is likely to have its own established governance already in place, CRN governance will need to operationally include and integrate the appropriate alliances across its components in order to be successful. The National System will thus need to be one that actively encourages a culture of collaboration and independence within specific disease-/device-areas.

CRN component registries and data sources are likely to include many of the entities previously described in this report, such as national professional society registries, PSOs, health systems, claims data and the like. Existing examples of these components and their current governance structures are useful to understanding the range of models a CRN would need to include and integrate into its governance structure. Such a governance "structure of structures" may not only capture efficiencies that facilitate operational processes but also allow the CRN to orchestrate inclusiveness across various stakeholders in governance of either the CRN itself or any participating component registry. Typically society-run registries are governed by a steering committee drawn from the society's membership that reports to executive- and board-level leadership for approval of mission, scope, policies and budget. The steering committee may create advisory groups of stakeholders, including patients, industry and health system representatives. The steering committee may also create subcommittees or task forces to manage specific aspects of registry operations such as publications and presentations, data content and quality and provider relations. Society policies and practices inform the functioning of the steering committee, including its membership and priorities, which vary among registries. Larger registries are run by salaried professionals employed by a society to oversee registry operations.

This centralized structure offers certain efficiencies and a broad perspective to governance, as well as financial accountability. The leadership and steering committee membership typically have defined policies and practices. Members of subcommittees, task forces, advisory groups and stakeholders know the steering committee membership and can be efficient in their communication. Such efficiencies may also constitute limitations to be overcome for more broadly based systems, e.g., those crossing different clinical specialties or national boundaries. Another drawback may be that single entity governance may engender outsider distrust, particularly if attached to a lucrative business model or influential publication resources unless special efforts are made to promote transparency and inclusiveness. Participation in a strategically configured CRN could identify avenues to mitigate such limitations through the CRN governance structure without necessitating changes to the governance within its participating entities.

Registry consortia (such as ICOR) have adopted a distributed model of governance. The distributed structure offers more independence, more diversity in approaches and broader engagement of established registries. A registry may delegate many governance functions to regional councils, which may choose different topics for their focus and employ different approaches to the same issues. This structure has the advantage of allowing small-scale experience to be gained with different approaches and, because the regional councils are represented at the national governance level, those learning experiences can be shared broadly. The distributed model may create more participants with firsthand knowledge of registry operations, including governance and financial responsibilities, thus increasing the expertise of individual members and creating depth in managerial skills. Distributed leadership may also provide society members with more understanding of and commitment to quality measures and care improvement.

The distributed model of governance may prove to be advantageous in addressing regional differences in health care practices, cost and outcomes that have been well documented by The Dartmouth Atlas for Health Care over many years.[2] For regional participants it offers better, faster communications with known members; for national stakeholders, it creates the need to communicate with more than one regional council on the same issue and may give rise to inconsistencies in practice and policy. ICOR's distributed governance approach has promoted a distributed data compilation capability that promotes a unique and robust approach to orthopedic device surveillance and safety signal detection. Participation of a distributed model such as ICOR in a CRN might enable a progression to patient-level data compilation for more expansive benefit/risk evaluations.

Thus the MDRTF concludes that CRN governance models 1) will vary across CRNs strategically intended to optimize device evaluation capabilities across the broad range of medical devices, 2) will be expected to operate within the umbrella of a larger governance system, e.g., the National Medical Device Evaluation System, 3) will require significant independence from the National System governance in order to achieve its mission, 4) will need to involve and integrate existing governance systems within each of its participating components, 5) may efficiently open avenues of governance optimal to CRN activity in the National System without necessitating changes to existing governance models of registries participating in the CRN, 6) will open a novel spectrum of opportunities for inclusiveness and stakeholder involvement both within the CRN and across the governance structures of each participating component (text box) and 7) may promote important enhancements to data compilations capable of supporting both safety surveillance and more robust benefit/risk evaluations for medical devices.

PERSPECTIVE FROM THE TVT REGISTRY:
The specific nature of stakeholder collaborations and partnerships will be naturally heterogeneous across different registry programs. For example, collaborations between professional society clinical registry programs and stakeholders may be quite different than between health systems and stakeholders. As one reflection of this example, the TVT Registry has included multiple stakeholders in its governance, including multiple professional societies, FDA, CMS, industry, academic research organizations, NIH, consumer and patient groups, and hospitals and health systems. Managing such multidisciplinary collaborations has presented challenges for the TVT Registry, but they are considered critical to its long-term success in having a role in both postmarket and premarket activities.[7]

Patient Interfaces

While the MDRTF CRN proposal is positioned to maximize registry and data repository networks for device evaluation, it is important to highlight how CRN structure promotes multiple avenues of patient engagement unique in the history of regulatory medical device processes. Patient advocates and organizations may engage the CRN directly or through any of its component organizations. At a governance level, and in concert with the CRN sustainability mission to deliver value to stakeholders, patients may ensure that data compilations and analytical efforts provide information that they seek. Strategically-configured CRNs may include sources of patient-reported outcomes or novel technology applications for patient reporting along with more traditional procedural specifics and clinical outcomes provided through device registries or EHRs. Thus the CRN structure promotes a flexible and evolving opportunity for incorporation of patient perspectives into benefit/risk device evaluation processes, and also ensures that such evaluations will include not only regulatory decisions but also deliverables specific to patient interests. In this way the CRN structure also promotes trust through participation and transparency, and enhances the likelihood that patients will recognize the value of permitting their personal data to contribute to the National Medical Device Evaluation System.

Beyond this, other methods should be considered for promoting transparency. CRNs should have publicly-available websites that provide information that patients can understand, and detailed information about the data that is useful for researchers. CRNs should also require every research project to produce a patient-facing summary on their website. The website should develop functionality to promote communication. For instance, when patients are enrolled in a registry participating in a CRN, the investigators should inform them of the website where additional information is available and where research will be posted. Patients, or anyone else, could then go to the site and sign up to receive emails concerning new research projects of interest. The CRN should also consider making its data available through an application-programming interface (API) to promote consumer engagement and novel ways for understanding and visualizing the information. This would also promote transparency and confidence in the information published.

Informed Consent

Clinical registry data is often collected as a part of an institution's quality assessment and improvement process, which does not require written informed patient consent. Indeed, the degree to which patients are aware that their procedure and outcomes information is being included in a registry varies greatly. Collection of protected patient health information, whether or not explicitly for research purposes, is a transaction involving detailed descriptions of how the data can be used, by whom and for what purposes. If research is one of the purposes of data collection, the Common Rule, IDE regulations, and various other Health and Human Services and FDA guidances may apply. If there is no research purpose, the transaction is governed by the Health Insurance Portability and Accountability Act of 1996 (HIPAA**)** Privacy Rule, which provides federal protections for individually identifiable health information held by covered entities and their business associates and gives patients an array of rights with respect to that information. The HITECH Act, which was designed to promote the adoption and meaningful use of health information technology, is also relevant. Subtitle D of the HITECH Act addresses the privacy and security concerns associated with electronic transmission of health information, in part through several provisions that strengthen the civil and criminal enforcement of HIPAA rules. In some instances, additional state-by-state provisions apply.

In either scenario, the documents are dense and defy comprehension by most readers. The variety of approaches defining what is research and what is quality improvement and the use of informed consent must be a focus for both the CRN and National System governing entities as the considerations transcend legal requirements.

The Belmont Report[4] and other sources indicate that patients support medical research if they understand its purpose and are provided information relevant to their diagnoses.[5,6] Patients are also motivated to participate in medical research by a desire to help others. Not surprisingly, patients are concerned about data security and privacy and uses of data that may harm them or their families, such as being excluded from health insurance. [7,8] Lingering distrust about any aspect of personal health information being collected for organized reporting is a critical issue

for CRNs and for the National System to explicitly address in its mission, operational design and deliverables.

Because traditional registries often collect information that is stored and may be accessed at a later time for purposes not defined at the time of collection, a lack of clarity exists regarding appropriate research protections generally and informed consent procedures specifically. Key ambiguities include whether informed consent is necessary for a postmarket registry or when patient information may be accessed for new or different purposes. What is required when information is used as the control arm in a prospective or retrospective study? Must patients have given prior consent to be contacted for longer term follow-up? Must information collection and informed consent comply with device-specific research regulations, such as the IDE regulation (21 CFR 812), if used for safety evaluation or effectiveness research or to support labeling changes?

Technology has also raised new questions about old elements of informed consent. Current technology allows direct contact with patients and could provide patient-reported outcomes to longitudinal research. New technologies may allow ongoing patient contact such that opting in or out becomes practical. Such technological advances give new meaning and raise new questions about the informed consent standard while raising new issues of patient engagement for registry governance which are clearly relevant to CRNs and the National System as a whole. Novel methods for data collection and engaging patients in the evaluation and surveillance of medical devices are developing rapidly. Patients can register for any number of patient-empowered research networks, such as those established by the Patient Centered Outcomes Research Institute, or other electronic data collection systems. As discussed in previous chapters, common data elements for collecting medical device data, particularly UDIs, should be established to decrease the heterogeneity of the quality of data being collected. Beyond this, new methods for conducting medical research will continue to develop with the proliferation of consumer products such as smart phones or wearable technologies that can capture medically relevant information. Many of these devices are equipped with powerful processors and sensors that can monitor movement, take measurements, and track information that can be valuable for medical research. In addition to sharing passive data associated with these devices, participants can contribute more patient-centric information, such as outcome measures or changes in disease symptoms, with better frequency and regularity. With these new platforms, patients who otherwise may not have participated in device registry because of geographic barriers, lack of awareness or inconvenience can provide robust and meaningful data.

Even as the MDRTF recommends sustainable CRNs should be tasked with ongoing recalibration of risk models, it is also recommended that CRNs should consider developing continuously updated applications and feedback portals for patients to directly contribute and control their health data. These applications can streamline the consent process, increase patient autonomy, rapidly disseminate research findings, notify users of new safety concerns, alerts or recalls, improve transparency of how data is being used and decrease the administrative burden and expense usually associated with contacting patients.

Developing a CRN-based national medical device evaluative system leveraging existing registry efforts through dual purposing has enormous pragmatic and cost efficiencies, but dual purposing potentially compounds the complexity of informed consent and related ethical obligations to patients about how their health information is being used. Quality registries capturing 100% of selected hospital procedures are unlikely to embrace dual purposing if informed consent requirements add work for staff and lead patients to decline to participate.

Thus the definition of clinical research generally, and informed consent and privacy permission requirements specifically, requires reexamination and clarification to support the development of CRNs and of a National Medical Device Evaluation System involving electronic information repositories such as registries. As mentioned in Chapter 5, that issues to be addressed, including benefit/risk profiles and thresholds for safety, will also vary across therapeutic areas and medical devices. The reexamination should take stakeholders into account both in addressing the paradigm of a learning health care system, which posits a continuous improvement cycle based on data collection and analysis, and with the likelihood that registry information will be used for purposes that are undefined at the time of collection. Patients in particular must be engaged in the review of research definitions, specifically informed consent, and in the development of new informed consent requirements.

For example, a learning health care system is clearly different than individual studies, which can be succinctly described in informed consent documents. Considerations of this and other changes to current research rules and regulations, including informed consent, to allow future undefined uses including regulatory applications, are essential to assuring patients that they have control over their health-related data. The issues of knowledge, control, privacy and trust are central patient-level concerns reported in the medical literature and defined by medical ethicists that will need to be addressed if CRNs are to accommodate the most critical stakeholders of all, patients, in promoting and protecting the public health. Recognition of new ethical responsibilities by FDA, patients and other CRN stakeholders in ongoing efforts such as those summarized in the January/February 2013 Hastings Center Report, Ethical Oversight of Learning Health Care Systems, is perhaps the best way to create critical momentum for these changes, as summarized in Panel 4 below.[8]

Panel 4. Ethical Oversight of Learning Health Care Systems
The Hastings Center Report recognized the blurred distinctions between research activities and quality improvement and the different standards for informed consent. It stated the goals of an ethical framework for a learning health system as (1) to increase the likelihood (ethical good) that continuous learning occurs, and (2) to ensure that this learning proceeds in an ethically acceptable fashion (appropriately protecting rights and interests). The report recommends wide disclosure that learning activities are occurring and assurances that confidentiality will be maintained. It includes the following seven obligations:

1. Respect the rights and dignity of patients and families
2. Respect the judgment of clinicians
3. Provide each patient optimal clinical care
4. Avoid imposing non-clinical risks and burdens
5. Address unjust health inequalities
6. Conduct continuous learning activities (clinicians and health care institutions)
7. Contribute to common purpose of improving quality and value of clinical care (patients & families)

With its many avenues of patient engagement, the CRN structure seems well positioned to advance this dialogue toward a more appropriate, contemporary and collaborative approach that protects patients and privacy while facilitating device evaluation. Clearly if a registry-based randomized trial involves an investigational device, classical informed consent rules should apply. For longer-term integration of patient procedural or outcomes data into a registry that participates in a CRN, a clearly written section might be included in the standard consent form, potentially with an opt-out check box. As the boundaries between clinical care and clinical research blur, and the value of a learning health system continues to emerge, the CRN structure is well suited to a better balance of stakeholder dialogue and more enlightened and trustworthy avenues for informed participation.

Privacy

Much has been written about privacy concerns in health research that need not be duplicated here.[9] Data privacy can be addressed in at least two different ways: data security and data selection and management.

Data security through changes to hardware, software, internet protocols and internet security is an activity that spans government and industry and has direct benefit to the healthcare industry. Decisions made in the selection of data, such as minimally necessary data sets that collect only key information, also serve to manage privacy concerns. For instance, distributed data storage and ownership help minimize potential for data privacy breaches. Limited access to data collected, under specific terms and conditions that patients have participated in defining, adds to trust in processes ensuring appropriate data privacy and security. Patient participation in reviewing proposed research assures that data will be used in a manner that does not harm patients. These practices are key to ensuring that patients will allow data collection over time. Conversely, breaches that result in harm to patients can have long-term consequences as the public distrust may linger after a particular incident is resolved.

CRN execution is likely to necessitate informatics-based solutions such as component registry linking or data extraction protocols. While challenges in interoperability and defining core minimum data sets will be encountered, CRN solutions are envisioned as complying with established privacy standards.

Access to Data

The traditional premise of registries is that knowledge useful to improving healthcare outcomes with medical devices can be derived by analyzing the collected data. The CRN structure elevates this premise, overcoming individual registry inadequacies by strategically linking multiple registries and data resources that complement one another to enhance benefit/risk analyses.

Most component registries will have existing policies and procedures that govern access to data for research and quality improvement purposes. These policies adopt different approaches to balancing the desire to share results with the need to assure that adequate data has been collected to be meaningful and that high-quality analysis is performed. Existing registry models for data access should be informative to how CRNs approach similar issues. Some registries, for example, allow researchers to access data directly, some at a patient level and some at an aggregated level. Others require researchers to submit questions, and the registries delve into the data themselves to provide a response. Still others mandate that any direct data access and analysis must be accomplished through designated personnel at designated centers. Some limit access to certain types of data (quality measures) to participants, while others allow access to non-participant researchers if specific conditions are met. The diversity of policies is even broader in registries that have distributed data storage and management. Many registries charge fees for data access or analysis.

Patient or lay access to data is evolving. The Task Force is unaware of device registries that currently provide patients direct access to their records or provide routine reports to patients. Such reporting is a goal of patient-powered research networks funded by PCORI and currently under development. Requests by lay individuals not in the registry about health outcomes derived from registry data are routinely denied.

Healthcare institutions, such as hospitals or health systems, and physicians who participate in registry data collection generally receive regular reports containing quality measure information. This information is used by institutions to benchmark their performance, to identify areas of potential quality improvement and for reporting purposes to governmental and accrediting organizations. The utility of registry data for institutions is critical to registry sustainability, as most fees supporting registries are paid by providers. Interviews with institutional and individual providers indicate that there is a wide variety of practices relating to the availability of quality measure data beyond standardized reports.

Industry participants report varied access to data. In most cases, industry receives reports about its own products against an aggregate benchmark of all other similar products in the registry. Industry may have access to only select or aggregated data. Access for industry to

patient- or provider-level data varies between registries. Ideally, industry support and participation will be documented in contracts that spell out access and provide industry with the information needed to fulfill regulatory requirements such as completion of post-approval studies, adverse event reporting and other regulatory obligations. It remains to be seen how frequently or efficiently industry stakeholders will be able to use information from CRNs to modify device labeling or provide evidence of safety and effectiveness, although this is one of the express intentions of the CRN structure for the National System, supporting more robust analytics along with cost and time savings. Real time safety signal detection approaches developed for postmarket surveillance might find other novel applications, such as being applied as an automated mechanism supporting data safety monitoring committees overseeing registry-based randomized studies of investigational devices.

Government agencies, such as FDA and CMS, are also consumers of registry data in some circumstances, traditionally for safety signal detection or confirmation but more recently also for IDE studies. Information dissemination to these stakeholders is likely to be a high priority, both because of the funding they provide and because of the impact HHS can have in the healthcare market. However, levels of data access and the ability to conduct direct queries and analysis vary between registries and agencies. This is another setting that may lend itself to a hybrid model, where a safety surveillance or quality metrics-focused registry might be used in conjunction with data from a distributed data architecture network to provide regulators with unique information. In developing a CRNCRN system and defining appropriate information, access and updates for federal agencies are clearly priorities.

Practices surrounding information dissemination will be affected by the expanding universe of clinical, payment and product utilization decision makers that the US system now has. Many market participants have access to data from a variety of sources and the ability to analyze that data. The availability of data is likely to increase, as is the ability of varied parties to provide analysis. It is likely that CRN data relating to medical devices will be one but not the only source used by key decision makers in both the market access and payment contexts. Society-based registry policies regarding information and dissemination are more oriented toward traditional academic concerns such as publications, presentations and quality measures than toward payers. As payers are key stakeholders in the innovation environment, thought should be given to understanding payer (including private payer) needs for outcomes and potentially economic data.

The challenge facing registry governing bodies includes understanding stakeholder ambivalence about the utility of registry data versus the danger of large amounts of centralized or linked data if used irresponsibly. A key responsibility of governing entities will be the successful reconciliation of differing points of view about the definition and operational logistics of responsible data use and dissemination. Significant to the outcome of such deliberations is likely to be whether they are developed within CRNs and a National System that promotes an atmosphere of inclusiveness and trust.

The proposed CRN structure is the most efficient and informative way to transcend the limitations of individual registries while leveraging their strengths. This implies that CRNs will not only compile data across registries or extracted from registries and other data sources into novel data sets for benefit/risk or safety signal analyses, but that CRNs will develop to accommodate aspects of stakeholder engagement and information access that are unique relative to their individual participating registries. Along these lines CRN governance will thus need to evolve data access policies unique to the CRN data sets.

The MDRTF recommends that data access policies, like data analysis deliverables, should be tailored to the specific values and needs of particular stakeholders. Data access and data information about a given medical device will be different for regulators making decisions than for professional societies defining best practices or for payers determining cost-effectiveness and comparative effectiveness, all of which may be different from what patients want to learn about their devices. To avoid overt misuse of data, the CRN emphasis for data access to CRN data sets should be the development of user interfaces, ease of use and tools tailored to support the highest value deliverables for each specific stakeholder group.

Dissemination and Transparency

Medical device research and surveillance is intended to increase knowledge and advance the public health. Traditional dissemination by the medical literature serves some but not all stakeholders. Patients, for instance, may want information about what has been learned and what they can expect from their device or condition in lay terms as well as lay summaries of broader research as available. Furthermore management of the way in which information about device benefit/risk and safety is disseminated should be a very high priority for CRNs and for the National Medical Device Evaluation System, as currently the lay public's first exposure to such information is via sensational media headlines. For the National System as a whole, the heterogeneity of therapeutic areas and medical devices makes information dissemination and context management problematic. At the CRN level, however, both specific focus and enhanced stakeholder inclusiveness provide a more pragmatic decision-making structure.

Intellectual Property and Related Legal Considerations

In the United States, intellectual property (IP) rights are exclusive rights arising from the ownership of patents, trademarks, copyright and, in most jurisdictions, trade secrets. Intellectual property itself has been defined as any product of the human intellect that the law protects from unauthorized use by others. United States law accords ownership of patent rights to the inventor or creator of the IP who first reduces the invention to practice and files for patent protection.

Medical device registry data is not invented or created by human intellect and is not protected as IP under United States law. Rather, registries are collections of reports of patient or product attributes over time. Individual patient information included in a registry does not constitute IP (an invention or creation). CRN data sets are likely to be similarly regarded.

Hospitals and health systems and individual health care professionals who collect and provide patient information to CRN component registries also are not inventors or creators. It is difficult to see how contributors of information would be accorded IP rights in the United States.

Component registry owners may create and register a trademark that identifies the registry and have exclusive rights to that trademark. Persons who develop case report forms, or publish or present data from a registry, have the ability to copyright their work. Neither of these is likely to apply at the CRN level—in fact, if the CRN develops core minimum data set criteria the MDRTF recommends that these criteria be released into the public domain.

Entities that accumulate, store, provide quality assurance services for and query or analyze data do have the ability to invent or create IP in the form of products or methods. These products or processes may be software, software applications, hardware or methods for data management and use. If this role is filled by professional societies, governmental or non-governmental entities or their employees or contractors, these entities may develop legally protectable IP arising from their role in registry management.

Similarly, persons who analyze outcomes or device performance may gain insight, and then may be better able to invent or create solutions to clinical problems that may be protectable as IP assuming all other relevant legal requirements are met. The ability to quickly and accurately analyze data sets such as large registries may provide a competitive advantage to individual device developers because, under US law, the person first making the invention or creation and reducing it to practice owns this IP. The development of better-performing devices or procedures leading to better patient outcomes is a desired benefit from the establishment of medical device registries, and data use for these purposes should be encouraged.

A related issue, although not technically IP, is confidentiality of data relating to a particular patient, provider, health system or product. Individual healthcare institutions, practitioners and device manufacturers may desire to use comparative registry data in marketing programs; conditions of data collection and individual registry policies will impact such uses. Open questions regarding confidentiality and data access remain regarding registry reporting to governmental entities, for example in the event of unanticipated or more frequent adverse events. Additionally, the use of registry data in litigation is a nascent concern of product liability and medical malpractice. Some registry structures, such as use of the Patient Safety Organization structure under the Patient Safety and Quality Improvement Act (2005), minimize this litigation risk.

Registries may contribute to public health by cost-effectively accruing a significant body of information about medical practice including medical device use that impacts patient outcomes. Intellectual property considerations need not be a barrier to registry participation for patients, providers, hospitals and health systems or industry as IP rights are very unlikely to arise solely from collection of registry data.

Thus CRNs are unlikely to develop or encounter critical IP, trademark or copyright issues beyond those already addressed in each of their component registries and data sources. Confidentiality issues are more likely to arise through varied perceptions of "responsible" data access, analysis and dissemination than through legal issues per se. In the broadly-based, collaborative environment of stakeholder participation envisioned for the CRN structure, these concerns can be addressed as described under Access to Data: Dissemination and Transparency.

Sustainable Infrastructure for Specific Applications

Historical perspectives on traditional registries for medical device evaluation raise concerns regarding the value of registry infrastructure vs its cost as well as the adequacy of data collection for device benefit/risk evaluation. The MDRTF recognizes such concerns to be intrinsic to the limitations of any single device registry, both in the content it is collecting and the infrastructure it provides. The CRN structure is proposed as the solution to such controversy 1) by strategically coordinating registries with complementary data content (short-term procedure-intensive linked to long-term follow up) to enable more informative benefit/risk evaluation 2) by strategically leveraging existing components (registries and data sources) for device evaluation rather than building a central registry infrastructure and 3) by actively promoting inclusiveness and customizing high value deliverables across a broad range of stakeholders..

CRNs thus position the National System to respond robustly to traditional controversies about sustainable device registries. Recommendations that registries have a single use with clear analytic objectives stem from the perception of cumbersome data collections that are burdensome and costly without valuable deliverables. Short term-only registries, furthermore, fail to provide longitudinal information that supports a learning health system, such as the ability to re-calibrate risk models or to confirm safety signal mitigation by new devices. Dual purpose linking or extracting from existing registries and data sources in CRN structures promotes the ability to conduct each as needed, supporting both efficiency and highly valuable deliverables. Furthermore, the CRN structure promotes flexibility over time as key component registries or data sources may change—for instance, data currently available at professional society registries may in 5 years be more seamlessly extracted from EHR sources.

Chapter Summary Points

1. Patient participation is an essential component in all aspects of registry governance.
2. A key responsibility of governing entities is the successful reconciliation of potentially differing points of view about the definition and operational logistics of responsible data use and dissemination.

Pilot Projects

Pilot I

Develop Best Practices

Develop best practices for patient, industry, clinician, researcher, and other stakeholder engagement in CRN design and operations. These practices will need to be tailored to different types of CRN designs:

- For hybrid systems (distributed and centralized) by leveraging existing models
- For systems created from data elements seamlessly extracted from EHR, using centralized data models

1. disease/device focus	Engage relevant stakeholders in developing a process that assures meaningful participation in the decision making process. Including explicit consideration of the likely cost and likely value of the outcome to stakeholders. Develop best practices that can be tested across different registry systems and for both disease and device specific registries.
2. Immediate research question(s)	Survey current practices used by existing registries, and public and private entities such as PCORI, NIH, and private foundations to determine research priorities. Using those resources, develop a process that will assure the meaningful engagement of relevant stakeholders in the processes of creating, reviewing and refining research questions that will produce information of value to diverse stakeholders.
3. Stakeholders engaged	Patients, healthcare institutions and healthcare providers are the minimum stakeholders for any effort to develop best practices relating to CRN design and operations. If applicable, industry, regulators, researchers, and others may be appropriately engaged in the "best practices development" effort with the understanding that not every registry will include such stakeholders.
4. Existing national resources leveraged	AHRQ, PCORI, existing registries, PSOs, healthcare systems with significant registry experience (Kaiser), foundations (Pew Charitable Trust, Brookings), and other entities (IOM, AdvaMed) and as appropriate, existing international registries.
5. Efficiencies promoted	A process framework for stakeholder engagement that can be adopted for new registries will hasten the creation and use of registries. Creation of a repository of such processes would allow groups without extensive resources to accomplish the goals of this document.
6. Applied national standards & definitions	AHRQ

Pilot II

Re-examine Definitions

Re-examine the definitions of clinical research generally, and informed consent and privacy permissions specifically, to support the development of a CRN in the context of a learning health care system:

- Engage patients in a robust and meaningful review of research definitions with a special emphasis on informed consent requirements.
- Engage product and research regulators in a review of regulatory definitions and the regulations governing the use of personal health information, whether or not collected specifically for research purposes, including from device or disease focused registries, and from EHRs or claims data for pre and post market regulatory applications, including availability for evaluation of benefit/risk and safety signals.
- Engage organizations devoted to quality measurement in a review of HIPAA/HITECH requirements, and research definitions, to assure that information from PSOs and other quality related registries may be disclosed and used by stakeholders as contemplated by a CRN in the context of a learning health care system.

1. Disease/device focus	Not specific to a particular device or disease
2. Immediate research question(s)	May information from claims data, EHRs, and PSOs be used in clinical research relating to medical devices? How can standards for informed consent be modified to account for new, interactive technologies and uses of data unforeseen at the time of data collection? What changes will providers need to make to privacy permissions relating to EHRs & claims data to facilitate information sharing in a CRN? What information about data uses, and medical devices/disease treatment outcomes, do patients desire in return for the contribution of personal data?
3. Stakeholders engaged	Patients, Providers, Payers, Physicians, Regulators, Ethicists, Privacy Experts, Data Security Experts
4. Existing national resources leveraged	TBD
5. Efficiencies promoted	Seamless sharing of relevant health information across data sources with limited risk to all participants
6. Applied national standards & definitions	TBD

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Appendix B.

Proposed Pilot Projects

Pilot Maturity	Proposed Pilot Projects	CRN Adoption Issues Addressed
Initiated	• Registry Assessment of Peripheral Interventional Devices (RAPID)	• Development of Core Minimum Data Set • Integration of CMD across Registries • Creation of Registry Based Trial
Initiated	• The Study of Access site For Enhancement of ST-Elevation MI for Seniors: SAFE-STEMI for Seniors	
Conceptual	• Develop and coordinate the architecture of a National Medical Device Evaluative System.	• Unified NMDES architecture • Identification and inclusion of HIT system participants • Identification and inclusion of Registry Participants • Development of common analytic services
Conceptual	• Enhance and extend functionality of the Global UDI Database (GUDID) to include supplemental data (i.e., a Supplemental UDI Database, or SUDID)	• Define system governance • Develop approach to data acquisition, management and access, and technical infrastructure
Conceptual	• Develop methodologic standards to match patients across encounters via the UDI, specifically to enable long-term surveillance. • Create a resource for health information system vendor support and systems evaluation. This consultative function is to specifically assist health information system vendors understand and implement standards (e.g., common data elements, common data models, structured reporting, user-centric design, semantic interoperability, etc.) • Pilot grants supporting local implementation of components of a national device evaluative system: • Implement UDI in the health information systems of health enterprises, including supply chain management, procedure documentation, electronic health record, and billing systems. The focus is on seamless interoperability of the UDI from system to system, including having each system utilize GUDID and SUDID services for managing	• Best practices for data security and patient privacy • Harmonization and unification of a medicine lexicon related to device surveillance • Defining and using Clinical, clinical research and regulatory use cases as a mechanism to evaluate the pilot

	device-related information, along with the aggregation of clinical data using the UDI as the identifier. • Implement key harmonized common data elements applicable to the cardiovascular and / or orthopedics domains within and across the procedure documentation and electronic health record systems of health care organizations, specifically based upon the data elements of the corresponding national, state, society, health system, or other applicable registry. This anticipates the linking of health system level data and registry data with claims data and initiatives including PCORnet and Sentinel, in order to maximize longitudinal follow-up and incorporate patient-reported information. • Provide clinician-focused education, consultative services (e.g., vendor liaison services, change management services), and technical assistance for the implementation of structured reporting for procedures involving implantation of Class III devices. This will facilitate organizational change that improves local efficiency and effectiveness by streamlining data capture via integrating into the clinical workflow. This in turn enables contribution of high quality data to a medical device evaluative system. • Conduct a series of medical device comparative effectiveness studies in multiple areas (cardiac, vascular, orthopedics) to demonstrate the value of leveraging the medical device evaluative architecture. • Validate Medicare linkage algorithms using existing registries with long-term follow-up for potential application to US networks. This would provide the basis for a network of registries linked with external data sources for longitudinal follow-up to accomplish systematic medical device evaluation.
Conceptual	• CRNs should be designed in keeping with the broader landscape of linked registries. • Device CRNs should have the ability to link short-term clinical data with long-term administrative outcome and cost data. • CRNs should include elements for risk prediction of traditional outcomes as well as patient benefit. • Registry Accreditation: Develop registry standards (check list developed by NMDR team) and apply to exiting national, professional, state, regional, and institutional registries to determine where there are current gaps that need to be addressed for linkage and surveillance and to determine the feasibility of registry certification/accreditation. US total joint registries consist of various models and may be optimal for piloting this approach. • Use national/regional/ international registries infrastructure to assess new technology. MGH has developed an ARO with capacity to leverage existing international total joint replacement registries to conduct clinical trials more efficiently at reduced cost: potential mechanism to pilot new orthopedic technology.

	• Optimal integration of procedural and Medicare claims data for regulatory and reimbursement decision making involving innovative transcatheter mitral valve implants
Conceptual	• Development of CRNs related to the following device-based procedures should be undertaken: • Hip replacement devices • Knee replacement devices • Vascular procedures/devices (includes peripheral+ AAA+ carotid + vascular access/catheters) • Spine surgery procedures/devices • Cardiac valve replacement • Atrial fibrillation (AF) ablation procedures/devices • ICD/CRT implantation • Coronary Stents • Robotic and other less invasive surgery • Ophthalmic procedures/devices • Surgical mesh • Pilot grants for local implementation to support: • Focus on developing a high priority device registry, or linkage of existing registries that is current underserved by offering incentives to participate in development and/or contribute to enhancing exiting national/professional society registries • Collaboration with professional societies to development of registries for high priority devices lacking adequate surveillance. Leverage existing data sources for the framework of these registries.
Conceptual	• Approaches to simultaneously account for multiple sources of data heterogeneity within a coordinated network for device assessment should be evaluated. • Characterizing conditions in which component registry summary statistics provide unbiased estimates of device performance and when such summaries are biased. • Guiding principles to handling missing data in coordinated networks where data dimension is large should be developed and validated. • Empirical studies of the validity of pooling assumptions and the coherence of comparisons, determination of a minimum number of observations required, and approaches to representing uncertainty of the strengths of relationships in the context of label extensions and clearance of predicate devices should be undertaken and guiding principles derived. • Stakeholder utility “banks” should be created and validated; the use of the utilities in

	assessing post-approval device safety and effectiveness – particularly in signal detection algorithms – should be demonstrated. • A systematic assessment of learning curves for a broad group of medical devices and generalizable knowledge should be summarized. • Empirical studies of the extrapolation algorithms for assessing the safety and effectiveness of medical devices used in pediatric populations should be undertaken and guiding principles derived. • Create novel signal detection methods using data mining techniques and validate against current methods in established registries with the intent to expand to new registries or networks of registries and electronic data systems.
Conceptual	• Develop best practices for patient, industry, clinician, researcher and other stakeholder engagement in CRN design and operations. These practices will need to be tailored to different types of CRN designs • For hybrid systems (distributed and centralized) by leveraging existing models. • For systems created from data elements seamlessly extracted from EHR, using centralized data models. • Re-examine the definition of clinical research generally, and informed consent and privacy permission specifically, to support the development of a national medical device evaluative system. • Engage patients in a robust and meaningful review of research definitions with an emphasis on informed consent requirements. • Develop software applications or leverage existing software applications for patients to directly contribute and make decisions about the use of their data their health data that will to streamline the consent process, disseminate research findings, directly notify users of new safety concerns, alerts, or recalls while providing appropriate data confidentiality • Pilot a hybrid system that integrates data from a specific-purpose device registry model with information from other electronic data repositories (EHRs, patient generated data) into a hybrid collaborative CRN.