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Predictable And SuStainable Implementation Of National Cardiovascular Registries Infrastructure: A Think Tank Report from MDEpiNet

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Abstract

The Medical Device Epidemiological Network Initiative (MDEpiNet) is a public-private partnership between the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) and participating partners. The Predictable and SuStainable Implementation of National Cardiovascular Registries (PASSION) program is an MDEpiNet-sponsored program which aims to demonstrate the goals of MDEpiNet by using cardiovascular medical device registries to bridge evidence gaps across the medical device total product life cycle (TPLC). To this end, a PASSION Think Tank meeting took place in October 2014 in Silver Spring, MD, to facilitate discussion between stakeholders about the successes, challenges, and future novel applications of medical device registries, with particular emphasis on identifying pilot projects. Participants spanned a broad range of groups including patients, device manufacturers, regulators, physicians/academicians, professional societies, providers, and payers. The meeting focus included four areas of cardiovascular medicine intended to cultivate interest in four

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MDEpiNet Disease Specific/Device Specific Working Groups: coronary intervention, electrophysiology, valvular disease, and peripheral vascular disease. In addition, more general issues applying to registry-based infrastructure and analytical methodologies for assessing device benefit/risk were considered to provide context for the Working Groups as PASSION programs going forward. This article summarizes the discussions at the meeting and the future directions of the PASSION program.

Introduction

The Medical Device Epidemiological Network Initiative (MDEpiNet) is a public-private partnership (PPP) including US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) and participating partners. [1] The mission and objectives of the MDEpiNet PPP are focused on advancing the national medical device evaluation and surveillance infrastructure in concert with the application of novel analytic approaches to bridge evidence gaps in the medical device life cycle in order to better define device benefit/risk profiles, refine the pre to post-market evidence balance and ultimately improve patient outcomes. (Table 1) As a PPP, MDEpiNet promotes broadly inclusive collaboration with a pre-competitive focus on the medical device evaluation landscape. The goal of pre-competitive collaboration is to develop tools that advance regulatory science including the efficiency of regulatory decision making through processes applicable to broad device classes. Through uniquely partnered perspectives, expertise and resources, the PPP cultivates a unique environment to address the lack of nationally unified data, build effective collaborations, and advance methodologies to better synthesize outcomes and device performance information. MDEpiNet's historical focus on infrastructure and methodology and its potential to better use post-market data to streamline pre-market requirements is particularly timely in the contemporary era of rapid national and international proliferation of disease and device registries, electronic health records, and data resources. In conjunction with the escalating engagement in health IT infrastructure across stakeholders in the medical device ecosystem, this timeliness was central to MDEpiNet's evolution from its FDA-sponsored origin to its growth into a more broadly based PPP.

In the midst of such a rapidly changing health care environment, the sense of opportunity may be undermined by risk aversion in the absence of established predicates and successes. Thus the Predictable and SuStainable Implementation of National Cardiovascular Registries Infrastructure (PASSION) program was convened both to discuss some of these issues as well as to advance pilot projects to promote pragmatic directions.

Medical device registries are generally designed with specific objectives, such as to assess postmarket device related outcomes or to provide information for quality improvement, facility and clinician benchmarking, and individual patient risk prediction. PASSION aims to advance the MDEpiNet mission by exploring how such registries can also inform the benefit-risk balance of high risk medical devices and decision making throughout the total product lifecycle (TPLC). The emphasis is enhanced clinical trial infrastructure development. To achieve this goal, essential principles must be established that can be applied in both disease and device specific projects. To that end, MDEpiNet held a Think

Tank meeting in Silver Spring, MD, on October 15, 2014, to discuss the PASSION initiative and generate momentum for a series of four cardiovascular device and disease specific registry based Working Groups.* A variety of stakeholders were represented at the meeting (Appendix I) including patients, device manufacturers, regulators, clinicians, academics, professional societies, health care systems, and payers.

The meeting was broadly divided into cardiovascular subspecialty device areas: coronary intervention, electrophysiology, valvular disease, and peripheral vascular disease. The syntax of discussions was based on identifying key issues that do and do not work well in current device registries for evaluative purposes (e.g. barriers to using electronic health information infrastructure for FDA pre- and post-approval studies) and on identifying near and long term priorities related to those issues. In addition, participants discussed potential pilot projects aligned with priority recommendations, where “proof of concept” deliverables could facilitate the long term changes needed to achieve “better, faster, cheaper” device evaluation.

General Principles of Registry-Based Cardiovascular Device Evaluation

Aligning Stakeholder incentives & Other Overarching Issues of Registries for CV Device Evaluation

All stakeholders agree that while the investment of time, money, or other resources may be necessary, there is benefit in adopting a new model for device evaluation that could eliminate redundancies, improve information quality, shorten timelines to patient access, and enhance timely dissemination of newly updated research findings. [2] The directly realized benefit of such a model varies based on the stakeholders’ particular interests.

Recently, FDA has encouraged collaboration with the Centers for Medicare and Medicaid Services (CMS) including coverage with evidence development to incentivize the systematic use of registries for post-market evaluation of newly approved devices. For example, the coverage decision for implantable cardioverter defibrillators (ICDs) for primary prevention was contingent on the development of a post-market registry. The National Cardiovascular Data Registry (NCDR)-ICD Registry was created in response. The FDA has also made some device approvals (particularly for those products under the Pre-Market Approval [PMA] regulatory authority) contingent on post-approval studies which, in some instances, are nested in existing national registries as in the case of Thoratec’s Heartmate II left ventricular assist device which underwent post-market surveillance within the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Registry. [3] Professional societies such as the American College of Cardiology (ACC), the Society of Thoracic Surgeons (STS), and the Society for Vascular Surgery (SVS) have responded to these initiatives by adapting existing registries or by designing totally new registries (e.g., Transcatheter Valve Therapy [TVT] Registry for transcatheter arotic valve replacement [TAVR] or the Vascular Quality Initiative [VQI] Varicose Vein Registry [VVR]) to fulfill

*Audio recordings are available to the public here: https://collaboration.fda.gov/p997d38ht0g/, https://collaboration.fda.gov/p7f9tvazt9p/, https://collaboration.fda.gov/p6mwydkm2wy/

multiple needs including CMS mandated participation requirements, FDA mandated post-approval studies, quality improvement initiatives, and other applications.

Meeting participants agreed that strategic incentives or "carrots" would be more effective long term than CMS and FDA "sticks" for registry development and sustainability. Investment in a registry could be rewarded through creation of an enduring platform that makes future device surveillance and/or future pivotal studies more scientifically robust but easier and less expensive to perform. Importantly, CDRH experience has demonstrated that clinical data collected as part of a registry can fulfill post-approval study requirements and/or supplement available data for label expansion of existing devices.[3, 4] In addition, FDA and CMS parallel review could leverage high quality registries to improve the pre and post-market data balance to achieve simultaneous device approval and coverage decisions. One example of such coordination was in the TAVR space. Ideally such decisions could be continually informed by post-market evidence development, in alignment with contemporary concepts of a "learning health system." [5] Such information may also be useful to private payers and the patients they cover, but historically private payers have not invested in generating post-market evidence (other than notable exceptions such as Kaiser Permanente and Blue Cross in some states). Many questions regarding the optimal role of private payers in such a paradigm remain unanswered.

Predictable business models are also critical for the sustainability of registry-based systems for device evaluation. To date, individual site fees, industry support, and limited government seed funding provide the majority of the financial support for device-based registries. The long term management of costs, especially as government funding decreases over time, is a key concern for sustaining a device registry. Rules regarding how cost might be allocated across established manufacturers who have previously contributed to developing and supporting the registry and new entrants into the space are currently not predictable. In addition to sharing experience within a device space, sharing of experiences or "lessons learned" between mature and more fledgling device registry spaces may be beneficial, but the governance facilitating such interactions is not established. The spirit of collegiality among PPP participants may be necessary, but is not sufficiently transparent, sustainable or predictable as a standalone solution.

Moreover, the number and type of stakeholders in device registries may continue to evolve. For example, as they develop, accountable care organizations (ACOs) may have a substantial interest in registries designed to interact with electronic health records (EHRs), and the role of these organizations in providing future support for medical device registries will evolve. Registries must be nimble enough to adapt to these varying and evolving needs of stakeholders, but clearly successful examples of device registry efforts along these lines have not yet emerged.

In addition to industry support of device registries, practicing physicians, hospitals, and non-physician practitioners and support personnel have provided much of the resources for data entry as well as fees for data reports. Thus if registries are to serve a dual purpose including use of data for benefit/risk evaluation, data accuracy and quality are essential. Therefore, incentivizing and simplifying input of information is critical. Currently, data capture for

device registries at the site/hospital level is perceived as burdensome. Such burden may potentially be reduced by better integration of data collection with workflow, including attention to issues of data accuracy and completeness in the clinical record. Additionally, physicians will remain dependent on timely bidirectional communication from registries to receive vital clinical feedback and to justify the investment required for ongoing registry operations. For instance the Vascular Quality Initiative is an illustration of how registries providing feedback to sites can lead to improvements in clinical practice. [6]

Another case in which feedback to providers is critical is in clinical contexts where providers have a variety of clinical backgrounds. For example, devices for peripheral vascular disease are used by radiologists, cardiologists, and vascular and plastic surgeons, and these different provider groups may adhere to different professional guidelines. Therefore, practice patterns are likely to vary more than in single profession clinical practice areas (e.g., coronary intervention) and such variation may impact operator proficiency, device performance, or both. A device registry may provide an opportunity for physicians to work together to develop clinical evidence and best practices across specialties and patient populations. Such cross-specialty cooperation and collaboration is already evident in the TAVR space in the use of “Heart Teams” to provide multi-specialty assessment of the patient prior to therapy selection.

Patients also stand to gain both directly and indirectly from the improved use of registries for studying medical devices. In some disease states (e.g., Duchenne’s muscular dystrophy) patients have generated and maintained registries.[7] The same could be done in device-specific realms. Of note, however, there is huge variability among patients regarding preferences around the sharing and studying of health information. [8] While most patients are willing to share their data, they want to know how their data are being used, what progress is being made, what information is being learned, and how the new information may impact care. What level of informed consent is warranted relative to how a patient’s data are used as part of a registry remains controversial. This highlights the need to involve and to effectively communicate information to all stakeholders including patients while assuring that the individual privacy of patient data in registries is maintained. [8]

In summary, there is growing recognition among stakeholders that there are opportunities for enhanced safety surveillance and for improved efficiency to achieve the “better, faster, cheaper” device evaluation goals. The PASSION Think Tank meeting is one embodiment of that shared vision.

Registries, research, and routine clinical care

With the emerging exception of pragmatic clinical trials[9, 10], a distinction has developed between clinical practice and research, leading to many examples where the same data are entered into clinical records or into case report forms by different staff. Indeed, many current statutory and regulatory policies govern research and clinical practice separately, or are at least interpreted as having such intent.

However, in many cases this division seems arbitrary and redundant, and actually inhibits information accrual about devices over time. For example, a substantial part of clinical

practice involves the off-label use of devices which may be associated with less well understood safety and effectiveness profiles, and outcomes from off label use are typically not captured in a systematic way. On the other hand, all studies in which data are collected prospectively to examine the safety and effectiveness of a new device (or of an existing device for a new indication) are considered research, and require ethics committee review, explicit informed consent and often an investigational device exemption (IDE) from FDA. [11, 12] "Dual purpose" registries have the potential to help integrate clinical research and clinical practice by informing both from a single infrastructure. [13] For example, the collection and analysis of existing de-identified clinical information from off-label use of medical devices captured in registries has been "reused" or "repurposed" to inform some regulatory decisions such as label expansion, as in the case of non-iliofemoral delivery of the transcatheter aortic valve using the TVT Registry. [4] In addition to some successes, this early experience has exposed some of the associated ethical, legal, financial, and informatics challenges of adapting clinical practice data for research and vice versa.

One major division between clinical research and clinical practice is the requirements for informed consent. In the course of medical practice, explicit consent is routinely obtained for minor and major procedures regardless of the quality or quantity of the evidence base or whether the procedure represents an FDA approved use of a device. For example, after obtaining customary consent, drug eluting coronary stents are routinely used to treat acute ST-elevation myocardial infarction based on an extensive body of evidence and authoritative professional guidelines[14] even though the only drug eluting stent approved for this indication is no longer manufactured. In other cases of off label device use in clinical practice, the evidence base is less established (e.g., use of the LARIAT device for left atrial appendage occlusion)[15], but the informed consent process may be similarly routine. In another example, registry data clearly intended to support ongoing evaluations of device benefit/risk such as for ACC/STS TVT and NCDR ICD registries are collected as quality data, with no explicit informed consent process. These discrepancies highlight how the informed consent requirements may seem arbitrary to providers and patients.

However, ethical issues arise when consent is sought for clinical research. For one, there are differing opinions about the appropriateness of the caring physician seeking consent for research. This may be heightened in a setting in which physician and/or hospital payment is contingent on participation in the registry/clinical trial (e.g., ICD implantation for primary prevention). Such new paradigms of research may require statutory and regulatory changes which typically take years. Currently, investigators must comply with informed consent requirements from local institutional review boards (IRBs), the FDA, Department of Health and Human Services (HHS), institutional policies, etc.; these policies are not always well aligned, and requirements are not static. [16,17] Importantly, there is ambiguity regarding how to build consent into registries to include consent for possible future "unknown" studies in which foreseeable risks may not be clear.

Furthermore, there is evidence that when explicit consent is sought, selection bias is introduced and the resulting population may be fundamentally different than the intended population. [18, 19] In some cases waivers or alterations of informed consent may be applicable especially in the case of "usual" or "standard of" care investigations, but these

issues are as yet unsettled. [20] A number of efforts are underway by various governmental, private, and academic groups to address issues of informed consent in clinical, routine, or standard practice that are outside the scope of the PASSION cardiovascular registries programs. [9, 16, 21–25]

In addition to ethical issues with informed consent in a registry setting, there are also concerns related to workflow, culture, and expectations from patients, providers and hospitals. It is unclear whether research-style informed consent could be efficiently incorporated into usual practice. [19] Moreover, resistance may be met from busy clinicians who may not see any direct benefit from participation. If PASSION is successful and dual purposing of registry data can add an efficiency of single data entry that provides both quality and outcomes data of interest to patients, the hospital and the practice community, then this could make the case for direct benefit from the contributing clinical practices with only modest changes in workload.

Data Standardization

In order to incorporate registry based research into clinical practice, there must be efforts towards data standardization from both the data element definition and data interoperability standpoints. One potential way of addressing this would be to standardize a core minimum data set that is device/disease specific to provide an acceptable level of safety and effectiveness evaluation. Indeed, there are many data elements common to data collection forms used in registries and case report forms used in clinical trials (irrespective of device or even across medical disciplines). There is precedent for the standardization of definitions as demonstrated by the Academic Research Consortium (ARC) and the ACC/AHA. [24–27] Other coalitions have also managed to standardize definitions for the purposes of moving towards data interoperability (e.g., INTERMACS and Japanese registry for mechanically assisted circulatory support [JMACS]).

Improving system interoperability would be a major advance in reducing the cost of registries. A vision of the future includes seamless interoperability between electronic health records and registries such that primary clinical data directly populate significant portions of the registry. However, the vast heterogeneity of information sources and data structures among current EHRs and registries limits any immediate execution of such a concept at this stage. Other more limited models that still point to the completely seamless integration vision can be identified, however. For example, the distributed data network model has been effectively applied internationally for this purpose (e.g., international collaboration for surveillance).[28, 29, 30] Distributed data networks address data standardization and interoperability issues through the use of common data models as in FDA's Sentinel Initiative, the Observational Health Data Sciences and Informatics program (OMOP), and the International Consortium of Orthopedic Registries (ICOR). [31, 32] In the future, the incorporation of unique device identifiers (UDI) in EHRs and registries could help further standardize core device-related information. Work related to UDIs, definition standardization, and system interoperability is ongoing through a variety of bodies including the Office of National Coordinator for Health IT, the National Library of Medicine, professional societies, the American Medical Informatics Association, the Pew Research

Center, Brookings and others. [33, 34] If each of these entities proceed independently the end-product and vision of a seamless medical device infrastructure will be much less likely than if partnerships such as the MDEpiNet PPP facilitate collaboration. For cardiovascular devices the PASSION program could potentially coordinate directions similar to other MDEpiNet initiatives in orthopedics, such as where FDA promoted several demonstration projects designed to develop a Global Orthopedic Device Classification Library of clinically meaningful attributes of orthopedic medical devices to supplement the Global Unique Device Identification Database (GUDID). The ICOR was instrumental in this project to ensure sufficient granularity of device identification in clinical registries. To date in the cardiovascular field, another MDEpiNet UDI demonstration project incorporated UDIs into data flow in a large US hospital system and resulted in the creation of the Supplemental UDI database of clinically meaningful attributes of coronary stents. [34]

Data accuracy, quality, and completeness

Data accuracy, quality and completeness are fundamental to any methodology of medical device evaluation, and the degree of readiness among data sources relevant to cardiovascular devices was discussed. In the current registry paradigm the accuracy of data elements is usually verified through intermittent auditing. For example, in the case of the NCDR, a recent data audit of selected data comparing data entered into the registry with medical record source information documented an accuracy of 93%. [35] Traditionally this is separate from the process of data monitoring common to clinical research, but these responsibilities could be efficiently blended in settings where national cardiovascular device registries purposed for hospital-based quality metrics could also be purposed for prospective registry-based research. The ultimate goal is to achieve integration of EHRs with registries such that the need for costly auditing is even further minimized. At the present time, however, that goal is distant.

Concerns were also voiced about the completeness of registry data, especially in regard to long term longitudinal follow up. Historically, US-based registries have lagged behind European counterparts since many European vertically integrated healthcare systems are more easily leveraged to provide longitudinal follow-up. In the US, on the other hand, most of the well-established cardiovascular registries provide very good procedural detail but follow up ends with discharge from the index procedure hospitalization. Significant progress has been made in linking such registries with Medicare claims data for long term endpoints such as death, stroke, myocardial infarction and rehospitalization. On the other hand there are very few systematic solutions to link procedural registries and long-term follow up data sources for the non-Medicare population, apart from a few selected third party payer registries. Even for Medicare patients, claims data have several limitations. First, most claims data are transaction oriented which makes it difficult to evaluate long term outcomes for specific brands or models of devices. While the integration of the UDI into claims processing is a promising approach to this limitation, this has not yet been implemented. Second, due to the legal interdiction on the use of personal patient identifiers in the US and the lack of the UDI in claims data, the linkage is indirect, and therefore must be derived by algorithm. Third, at present it is limited to diseases and related therapies which primarily or exclusively affect Medicare eligible patients. Fourth, linkage of any data sources can be very

costly due to separate costs of procuring the data and the technical expertise and resources needed to make the linkages. Fifth, Medicare data are generally available after a lag of about 18 months, and the codes that such linkage methods rely on are part of a revenue-based system rather than a clinical one illustrating that incentives for reimbursement and research are not always well aligned. Finally, despite a growing Medicare HMO population which now includes approximately 30% of Medicare beneficiaries[36], Medicare HMO data are not captured in a way that is directly available to researchers.

In some cases, completeness of registry data represents a tradeoff between inclusiveness and the burden of data collection. For example, the first version of the TVT Registry data collection form included over 350 individual data elements to address the varying goals of multiple stakeholders. The second version reduced the number of data elements by approximately 10% as a compromise between completeness, work load burden, and expediency. Further reduction in the number of fields will be guided by data requirements for risk prediction algorithms, adverse event monitoring, and refinement of benchmarking and quality improvement needs.

Timeliness and Work Flow Burden

Some features of existing registries are burdensome relative to clinical work flow, and where added steps are involved time delays may also ensue. Timeliness may be an issue for processes such as the translation of source information into data per registry specifications, the linking of registry data with other data sources that include longer-term outcome data, and in dealing with the bureaucracy of registry governance. Conversely, faster access to compiled registry data could benefit many stakeholders. For example, timely reports of adverse events and benchmarked outcomes data to practicing physicians may lead to faster consensus on best practices and safer and better care for patients. Delay in safety reports can increase risks to patients and financial exposure of manufacturers as well as potentially jeopardize public safety. Guidelines regarding how, when, and to whom reports from registries should be made available to the public are evolving.

From a practical standpoint, if a registry is administered by a third party (i.e., not the device manufacturer), there must be infrastructure in place to provide timely feedback to manufacturers while maintaining proprietary data firewalls where necessary. The issue of timeliness in reporting is made more complicated by the variability in defining timeliness itself – the pace of device innovation, the pace of regulatory review, the pace of peer review scientific publication, or the pace of coverage decisions span a broad range.

High priority timelines through the device TPLC for many stakeholders include the time from early feasibility testing to commercial bedside use, and the time from safety signal detection (post-market) to signal confirmation and dissemination. Approaches to these priorities include more routinely aligning the FDA approval and CMS coverage decision processes, but there are concerns that strategy may not be possible or efficient under current circumstances. Also, a predefined and/or prospective process of linking registry data to a longitudinal system of data collection may reduce the delay in obtaining and reporting longer term outcomes, both for safety surveillance and effectiveness evaluations. Lastly, a predefined process for the management and escalation of safety issues is critical to the

ability of a registry-based system to inform manufacturers and regulators with respect to public health responsibilities.

Statistical and methodological concerns

Just as there is need to innovate in trial design and infrastructure to achieve "better, faster, cheaper" device evaluations, innovative statistical and methodological procedures are needed to analyze and report the data. Data standards and requirements may differ based on the audience – regulators, clinical care providers, payers, patients, etc. In addition, there is extensive variability in the data contained in registries (and even more in the source information). Data across different registries may vary in content, definitions, completeness, design (prospective vs. retrospective, etc.), and types (natural language, claims/billing, etc.) among other variables. There is currently no one solution for handling this myriad of data quality issues, however there has been substantial progress in statistical and methodological science focused on harnessing the power of registries despite the heterogeneity across such data sources. For example, methods for linking registry data to CMS billing data have been demonstrated to be usefully accurate. [37] Of note, while CMS is the largest US payer overall and dominant in some specific device and/or disease areas, this type of linking may exclude other relevant groups. Moreover, CMS claims and claims data in general, are frequently inadequate to capture patient outcomes and are imperfect for many "softer" but important endpoints like quality of life, pain, dementia, and disability.

Innovation and advances in analytical methods (e.g., the use of instrumental variables, propensity matching, and Bayesian analysis) may also make it possible to use existing data for device research.[38] At present, for instance, it can sometimes be difficult to establish a control group for device studies. Historical experience has offered one potential solution in mature device areas (e.g., objective performance criteria), and with more data collected in registries, historical data can be more powerful and more nimble.[39] Another potential use of prospective registry data is matching at the time of procedural hospitalization to establish more meaningful comparisons, particularly when randomization is not possible.

In addition to being a source of observational data, registries can also serve as the infrastructure for prospective clinical trials. The NCDR-PCI Registry was used as the infrastructure for the Study of Access Site for Enhancement of Percutaneous Coronary Intervention (SAFE-PCI) for Women study which led to significant efficiencies, including faster subject enrollment and a reduction in overall trial costs. These experiences will be applied to the Study of Access site For Enhancing PCI in STEMI (SAFE-STEMI) for Seniors which will employ the same registry for a prospective randomized controlled study to support two independent IDE applications.[40] In a parallel effort, the Vascular Quality Initiative (VQI) will be used as the framework for a randomized clinical trial comparing open versus endovascular repair of popliteal aneurysms in the OVERPAR trial with a budget fixed at $10,000/year. [41] The VQI is a distributed network of regional groups that collaborate in regard to data collection and reporting with the goal of improving quality, safety, effectiveness, and cost of vascular health. [42] Partnerships between academia, regulators, professional societies and manufacturers were critical to study design for these studies and will lead to significant study efficiencies.

Priorities

With the above major issues in mind, a chief focus of the PASSION Think Tank was to generate concrete priorities for the near and long term.

Near Term Priorities

First, there must be a sustainable forum for ongoing dialogue between stakeholders for both device and disease-specific projects as well as those with more general goals. MDEpiNet's progression to a PPP and this PASSION Think Tank are steps in that direction. Lessons learned and best practices in the area of registry-based device surveillance and research need to be institutionalized and disseminated through these forums, the medical literature, and other networks in order to reduce duplication of work and advance the field. [43] The work of industry, not-for-profits, governmental organizations, academia, health systems, and patient organizations are all relevant to each other. [44–46]

Second, in order to achieve momentum, incentives need to be better aligned, and some of this can be done in the near term. For example, stakeholders can engage very early to align goals, budgets, timelines, and expectations to ensure that the data collected and reported meet the needs of stakeholders and to address questions such as: Will the evidence generated meet the evidence level required for FDA approval decisions? For CMS reimbursement decisions? For professional society endorsement and integration into best practice recommendations? For regulatory endorsement outside the US? This may mean more collaboration between manufacturers in order to support and use similar systems for data capture, transmission, and maintenance. Even as efforts along these lines move forward, they also raise important new questions. For instance equity issues need to be addressed – if a new entrant to a field gains benefits from an existing registry infrastructure built or supported by the first entrants into a field, issues of fairness may arise. On the other hand, if an existing device manufacturer has great influence over key areas of registry infrastructure for that device, then they may have the power to create barriers to entry for new competitive entrants. In addition, it remains unclear what role drug or biologic stakeholders should play in device registries when their interests are overlapping. For example, if a device registry for peripheral vascular intervention is financially supported by a stent manufacturer, what financial role should the manufacturer of an antiplatelet agent be required to play if that registry is utilized as the infrastructure for studying that drug? Aligning incentives is critical to achieving financial sustainability of registries for regulatory, public health, and business motivations.

Third, patients are currently only minimally engaged in registry development and conduct. Historically, the good intentions of other stakeholders were seen as a surrogate for actual patient involvement. It is clear now, however, that patients bring knowledge, perspective and experience that is unique and may be difficult to anticipate by traditional investigators, regulators, and other non-patient stakeholders. [47] Opportunities to more closely involve patients and patient groups in registry design and analysis were repeatedly voiced as a priority of the course of the PASSION Think Tank. One important way of doing this is to improve registry capture of endpoints that are important to patients such as quality of life, disability, cognitive function, and pain. Other stakeholders that could also be better

represented include: small device companies; EHR and other clinical software vendors; quality improvement and value analysis professionals; practicing physicians and clinicians who collect and manage registry data; research coordinators; and medical coders.

Fourth, “proof of concept” projects are essential in order to understand unanticipated pitfalls and consequences of registry operations and registry-based data analyses. While there are many issues to be resolved, much progress has been made; pragmatic and applied lessons learned from pilot projects were broadly considered the fastest and most informative way to propel the field forward.

Long Term Priorities

The long term vision of device based research involves the seamless integration of electronic health information that includes UDIs with a fully integrated research infrastructure which serves to eliminate the historical schism between clinical practice information and clinical research supporting device evaluation. A unifying lexicon of standardized endpoint definitions would help move towards such a paradigm in which source documents effectively serve to auto-populate case report forms. [24] Moreover, once there is a substantial body of experience with device registries, data from these registries could be used to develop, validate, and periodically re-calibrate objective performance criteria, risk models, and other efficient modalities through which new devices could be compared. Significant operational changes are needed to fully achieve this vision, with change also needed in healthcare delivery and even in the training of physicians. Small, short term steps and pilot projects toward this more seamless long term vision were generally endorsed by participants in the PASSION Think Tank.

Conclusion

Technological innovation in cardiovascular devices is proceeding rapidly. However, the current resource-intense device approval paradigm in the US is increasingly strained to keep pace globally, resulting in significant gaps in device approval and availability for US patients and physicians. Creation of a reusable infrastructure to collect medical device data throughout the total product lifecycle is an ideal solution for simplifying and streamlining data collection for regulatory approval and other purposes. As such, leveraging existing registry infrastructure linked to other electronic data sources and health records has the potential to offer a high quality, long term, efficient alternative model for medical device research throughout the total product lifecycle.

The PASSION program can serve as an incubator for projects falling within this alternative model in which existing national cardiovascular registries serve as the infrastructure to generate valid scientific evidence to make benefit/risk evaluations and regulatory decisions. This PASSION Think Tank led to formation of four cardiovascular device working groups where high quality professional society registries that are specific to each area exist. These include: the Coronary Stent working group (ACC NCDR Cath-PCI and ACTION Registries); The Structural Heart working group (STS/ACC TVT Registry, ACC IMPACT Registry); the Heart Rhythm working group (ACC NCDR ICD registry); and the Peripheral Vascular and Endovascular working group (SVS/SCAI Vascular Quality Initiative, ACC

NCDR PVI Registry). A fifth working group will focus on addressing general principles for cardiovascular device trials and shared infrastructure including governance, interoperability, contracting, etc., and ongoing issues as they are identified through proof of concept projects emerging from other working groups. Follow up reports from these working groups including proof of concept projects are planned for 2015 and beyond.

REFERENCES

1. Medical Device Epidemiology Network. 2015 Mar 25. http://www.mdepinet.org/
2. Krucoff MW, Brindis RG, Hodgson PK, Mack MJ, Holmes DR Jr. Medical device innovation: prospective solutions for an ecosystem in crisis Adding a professional society perspective. JACC Cardiovascular interventions. 2012; 5(7):790–796. [PubMed: 22814785]
3. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, et al. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol. 2014; 63(17):1751–1757. [PubMed: 24613333]
4. FDA approval expands access to artificial heart valve for inoperable patients 2013. 2015 Jun 15. Accessed at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm369510.htm
5. Olsen, LA.; Aisner, D.; McGinnis, JM., editors. The Learning Healthcare System. Washington DC: Workshop Summary; 2007. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK53494/
6. Cronenwett JL, Kraiss LW, Cambria RP. The Society for Vascular Surgery Vascular Quality Initiative. Journal of vascular surgery. 2012; 55(5):1529–1537. [PubMed: 22542349]
7. Rangel V, Martin AS, Peay HL. DuchenneConnect Registry Report. PLoS currents. 2012; 4:1309.
8. Institute of Medicine. [Accessed July 29, 2014] Committee on Health Research. Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research. The National Academies Collection: Reports funded by National Institutes of Health. 2009. Available at: http://www.ncbi.nlm.nih.gov/books/NBK9578/
9. Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. JAMA. 2014; 311(23):2381–2382. [PubMed: 24810723]
10. Anderson ML, Califf RM, Sugarman J. for the participants in the NIH Health Care Systems Research Collaboratory Cluster Randomized Trial Workshop. Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. Clin Trials. 2015 Jun; 12(3): 276–286. [PubMed: 25733677]
11. 21-CFR-50. Protection of Human Subjects.
12. 21-CFR-812. Investigational Device Exemptions.
13. US Food and Drug Administration Center for Devices and Radiological Health. Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval. 2015. Accessed at http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf
14. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013; 61(4):e78–e140. [PubMed: 23256914]
15. Chatterjee S, Herrmann HC, Wilensky RL, Hirshfeld J, McCormick D, Frankel DS, et al. Safety and Procedural Success of Left Atrial Appendage Exclusion With the Lariat Device: A Systematic Review of Published Reports and Analytic Review of the FDA MAUDE Database. JAMA Intern Med. 2015 Jul; 175(7):1104–1109. [PubMed: 25938303]
16. Office of Human Research Protections. Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care. Accessed at http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html

17. US Food and Drug Administration Center for Devices and Radiological Health. Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors. 2014. Accessed at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf
18. Kho ME, Duffett M, Willison DJ, Cook DJ, Brouwers MC. Written informed consent and selection bias in observational studies using medical records: systematic review. Bmj. 2009; 338:866.
19. Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, et al. Impracticability of informed consent in the Registry of the Canadian Stroke Network. N Engl J Med. 2004; 350(14):1414–1421. [PubMed: 15070791]
20. Kim SY, Miller FG. Varieties of standard-of-care treatment randomized trials: ethical implications. JAMA. 2015; 313(9):895–896. [PubMed: 25591061]
21. Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, Brehaut JC, et al. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLoS medicine. 2012; 9(11):1001346.
22. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An Ethics Framework for a Learning Health Care System: A Departure from Traditional Research Ethics and Clinical Ethics. Hastings Center Report. 2013; 43(1):S16–S27. [PubMed: 23315888]
23. Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. N Engl J Med. 2014; 370(8):766–768. [PubMed: 24552325]
24. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation. 2015 Jul 28; 132(4):302–361. [PubMed: 25547519]
25. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012; 60(15):1438–1454. [PubMed: 23036636]
26. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011; 123(23):2736–2747. [PubMed: 21670242]
27. Krucoff MW, Mehran R, van Es GA, Boam AB, Cutlip DE. The academic research consortium governance charter. JACC Cardiovascular interventions. 2011; 4(5):595–596. [PubMed: 21596341]
28. Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J, McClellan M. The New Sentinel Network — Improving the Evidence of Medical-Product Safety. N Engl J Med. 2009; 361(7):645–647. [PubMed: 19635947]
29. Sedrakyan A, Paxton EW, Phillips C, Namba R, Funahashi T, Barber T, et al. The International Consortium of Orthopaedic Registries: overview and summary. J Bone Joint Surg Am. 2011; 93(Suppl 3):1–12. [PubMed: 22262417]
30. IMDRF Work Item. Medical device single audit program. 2015 May 18. http://www.imdrf.org/workitems/wi-mdsap.asp
31. FDA's Sentinel Initiative. 2015 Mar 25. http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
32. Observational Health Data Sciences and Informatics Program. 2015 Mar 25. http://www.ohdsi.org/
33. The Office of the National Coordinator for Health Information Technology. Connecting Health and Care for the Nation: a shared nationwide interoperability roadmap. Accessed at https://www.healthit.gov/sites/default/files/hie-interoperability/nationwide-interoperability-roadmap-final-version-1.0.pdf
34. Tcheng JE, Crowley J, Tomes M, Reed TL, Dudas JM, Thompson KP, et al. Unique device identifiers for coronary stent postmarket surveillance and research: a report from the Food and Drug Administration Medical Device Epidemiology Network Unique Device Identifier demonstration. Am Heart J. 2014; 168(4):405–413. 2. [PubMed: 25262248]

35. Messenger JC, Ho KK, Young CH, Slattery LE, Draoui JC, Curtis JP, et al. The National Cardiovascular Data Registry (NCDR) Data Quality Brief: the NCDR Data Quality Program in 2012. J Am Coll Cardiol. 2012; 60(16):1484–1488. [PubMed: 22999725]
36. Medicare Advantage Fact Sheet. 2014. Accessed at Available at: https://kaiserfamilyfoundation.files.wordpress.com/2014/05/2052-18-medicare-advantage.pdf
37. Brennan JM, Peterson ED, Messenger JC, Rumsfeld JS, Weintraub WS, Anstrom KJ, et al. Linking the National Cardiovascular Data Registry CathPCI Registry with Medicare claims data: validation of a longitudinal cohort of elderly patients undergoing cardiac catheterization. Circ Cardiovasc Qual Outcomes. 2012; 5(1):134–140. [PubMed: 22253370]
38. US Food and Drug Administration Center for Devices and Radiological Health. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. 2010. Accessed at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm
39. Moore JW, Greene J, Palomares S, Javois A, Owada CY, Cheatham JP, et al. Results of the Combined U.S Multicenter Pivotal Study and the Continuing Access Study of the Nit-Occlud PDA Device for Percutaneous Closure of Patent Ductus Arteriosus. JACC Cardiovascular interventions. 2014; 7(12):1430–1436. [PubMed: 25523534]
40. SAFE STEMI for Seniors. A PASSION proof of concept study. 2015 Mar 27. http://www.mdepinet.org/wp-content/uploads/Oct_15_S3_1_Kong.pdf
41. Eslami MH, Doros G, Goodney PP, Elderup-Jorgenson J, Cronenwett JL, Malikova M, et al. Using Vascular Quality Initiative as a Platform for Organizing Multicenter, Prospective, Randomized Clinical Trials: OVERPAR Trial. Ann Vasc Surg. 2015 Feb; 29(2):278–285. [PubMed: 25311746]
42. Vascular Quality Initiative. 2015 Mar 25. http://www.vascularqualityinitiative.org/
43. Rajan PV, Kramer DB, Kesselheim AS. Medical device postapproval safety monitoring: where does the United States stand? Cir Cardiovasc Qual Outcomes. 2015; 8(1):124–131.
44. Medical Device Registries. Recommendations for advancing safety and public health 2014. Accessed at http://www.pewtrusts.org/~/media/Assets/2014/09/Device-Registry-Conference-Report.pdf
45. AdvaMed. AdvaMed Registry Principles. 2013. Accessed at http://advamed.org/res.download/397
46. Agency for Healthcare Research and Quality. Registries for evaluating patient outcomes: A user's guide. 2014. Accessed at http://www.ncbi.nlm.nih.gov/books/NBK208616/
47. Stolker JM, Spertus JA, Cohen DJ, Jones PG, Jain KK, Bamberger E, et al. Rethinking composite end points in clinical trials: insights from patients and trialists. Circulation. 2014; 130(15):1254–1261. [PubMed: 25200210]

Appendix I. PASSION Think Tank Faculty and Speaker List

First name	Last name	Organization/Affiliation
Academia & Practicing physicians		
Hussein	Al-Khalidi	Duke University
Sana	Al-Khatib	Duke Clinical Research Institute
Matthew	Brennan	Duke Clinical Research Institute
Jeffrey	Brinker	Johns Hopkins
Jack	Cronenwett	Dartmouth Medical School
Fred	Edwards	University of Florida
David	Feigal	Arizona State University, School of Law
Jessica	Jalbert	Duke Clinical Research Institute
Larry	Kessler	Department of Health Services, School of Public Health @ University of Washington

First name	Last name	Organization/Affiliation
Ajay	Kirtane	CUMC / New York-Presbyterian Hospital and Cardiovascular Research Foundation
David	Kong	Duke Clinical Research Institute, Duke University
Mitchell	Krucoff	Duke Clinical Research Institute, Duke University
Jack	Cronenwett	Society for Vascular Surgery Patient Safety Organization
Sharon-Lise	Normand	Harvard Medical School
Terrie	Reed	Duke Clinical Research Institute
Art	Sedrakyan	Weill Cornell Medical College
James	Tcheng	Duke University
Ron	Waksman	MedStar Heart & Vascular Institute
Joseph	Drozda	Mercy Center for Innovative Care
Industry		
Jodi	Akin	Hawthorne Effect, LLC
Sandeep	Brar	Medtronic, Inc.
Mark	Carlson	St. Jude Medical, Inc.
Robin	Eckert	Abbott Vascular
Neal	Fearnot	Cook Group Incorporated
Todd	Fonseca	Medtronic, Inc.
Kristi	Mitchell	Avalere Health, LLC
Robert	Thatcher	Cardiovascular Systems, Inc
Eric	Schorsch	St Jude Medical, Inc.
Ken	Stein	Boston Scientific
Roseann	White	Abbott Vascular
Food and Drug Administration		
Greg	Campbell	CDRH/OSB/DBS
Daniel	Canos	CDRH/OSB/DEPI
Owen	Faris	CDRH
John	Laschinger	CDRH/ODE/DCD
William	Maisel	CDRH
Jose	Morales	CDRH/ODE/DCD
Danica	Marinac-Dabic	CDRH/OSB/DEPI
Kathryn	O'Callaghan	CDRH/OCD
James	Saviola	OC/DBM
Mitch	Shein	CDRH/ODE/DCD
Murray	Sheldon	CDRH/OCD
Kimberly	Trautman	CDRH/OCD
Changfu	Wu	CDRH/ODE/DCD
Bram	Zuckerman	CDRH/ODE/DCD
Professional Societies		
Ralph	Brindis	ACC/UCSF

First name	Last name	Organization/Affiliation
Kathleen	Hewitt	American College of Cardiology
Michael	Mack	Baylor Healthcare System, Society of Thoracic Surgeons
Patient organizations		
Bray	Patrick-Lake	Patient representative
Private payer organizations		
Liz	Paxton	Kaiser Permanente
International		
Marie Claude	Morice	CERC (Cardiovascular European Research Center)
Kazuhiro	Sase	Juntendo University
Other		
Rosemarie	Hakim	Centers for Medicare and Medicaid Services
Julia	Skapik	Office of the National Coordinator for Health Information Technology
Elise	Berliner	Agency for Healthcare Research and Quality

Table 1

MDEpiNet mission, objectives and strategy

Mission:
To bridge evidentiary gaps, to develop datasets and innovative methodological approaches for conducting robust analytic studies to improve medical device safety and effectiveness understanding throughout the device life cycle.
Objectives:
• Improve how medical device information is utilized throughout the life cycle of a device.
• Synthesize evidence from pre-market clinical trials, post-approval observational studies, domestic and international registries, medical claims data, and published literature on how medical devices are used throughout their life cycle.
• Develop a conceptual framework for comparative effectiveness that examines relationships between and among medical treatments, patient outcomes, medical devices, resulting in development of novel study designs and analytical strategies, and application of these scientific advancements to CDRH regulatory decision making.
• Advance the development and testing of new approaches to medical device studies that address the device's life cycle.
• Collaborate as co-authors/peer reviewers to communicate MDEpiNet work results.
Strategy:
• Systematically evaluate and integrate evidence of risks and benefits associated with medical devices into regulatory science.
• Collaborate with external parties with relevant expertise to determine evidence gaps, study questions, datasets and best practices.
• Incorporate appropriate study designs, analytical strategies, and regulatory decision making to develop a framework for patient-centered outcomes in medical device study and regulation.
• Develop, test and disseminate innovative methodological approaches and study results in medical device research.
• Leverage partner resources and expertise to create a sustainable infrastructure that stakeholders can use to obtain knowledge about medical devices.
• Fully integrate the MDEpiNet infrastructure into CDRH decision making and the systematic evaluation of medical devices.