DISCUSSION PAPER: COORDINATED REGISTRY NETWORK FOR DEVICES USED FOR ACUTE ISCHEMIC STROKE INTERVENTION (DAISI)

FDA/CDRH Stroke Registry Network Working Group

Discussion Paper: Coordinated Registry Network for Devices Used for Acute Ischemic Stroke Intervention (DAISI)

Content

I. Introduction

Stroke is a debilitating disease that kills nearly 130,000 Americans each year and is the fifth leading cause of death according to the Centers for Disease Control and Prevention. The U.S. Food and Drug Adminstration is committed to fostering the timely development and approval of medical devices for patients with acute ischemic stroke. We seek to work with other interested parties to establish a Coordinated Registry Network (CRN) as described by the Medical Device Registry Task Force.[i] We are releasing this discussion paper in preparation for the upcoming public workshop, "Establishing a Coordinated Registry Network for Devices Used in the Treatment of Acute Ischemic Stroke." The FDA is hosting this workshop at the National Institutes of Health on February 2, 2017[ii] to facilitate discussion among interested stakeholders (e.g., manufacturers, health care professionals, patients, patient advocates, academia, hospital administrators, professional societies, payers, and other government agencies). Our objective of organizing a coordinated effort is to discuss the establishment, data elements, and sustainability (long term value) of a CRN for collecting evidence in support of medical devices used in the treatment of acute ischemic stroke, i.e., Devices for Acute Ischemic Stroke Intervention (DAISI).

The information contained in this document is not binding and does not create new requirements or expectations for affected parties, nor is this document meant to convey FDA's recommended approaches or guidance. Rather the information contained in this document offers background and the basis for discussions at the Public Workshop.

II. Establishing an Infrastructure for a Coordinated Registry Network

Protecting and Promoting the Public Health

CDRH is committed to fostering the development of high-quality, safe and effective devices of public health importance and facilitating access for patients to these technologies. The U.S. regulatory framework for approving or clearing medical devices that are introduced into the marketplace often relies on clinical data to support the "reasonable assurance of safety and effectiveness" of the device. Our framework also takes into account the benefits and risks for the target patient population. We believe there are at least six key incentives for establishing a CRN to help evaluate the use of FDA medical devices marketed in the U.S. They are listed below.

1. Enable the systematic collection of real-world evidence when medical devices are used in clinical practice.
2. Collect valid scientific evidence to support marketing submissions, when appropriate,
3. Aid in the identification of postmarket safety events so that appropriate surveillance and mitigation actions can be implemented.
4. Provide stakeholders time and cost savings by conducting or nesting clinical studies within the registry network.
5. Provide clinical data for use in research and scientific publications.
6. Provide quality data for use by hospitals and other health care facilities.

Clinical studies are typically conducted in a controlled environment with investigators who are familiar with, and trained in the use of the device. These studies can sometimes present challenges that increase the cost or time to completion. These challenges may be associated with the target patient population, prevalence of a disease or condition, or length of follow up necessary to assess the safety and effectiveness of a device. One example in studies for devices used in endovascular therapy (ET) is the low prevalence of stroke in the posterior circulation.

In addition, clinical studies of medical devices are generally not intended to capture the effects of operator experience, learning curves, or skill level of the physician or supporting clinical staff. These effects are usually not observed until the medical device is in widespread use.

National Evaluation System for Health Technologies

Over the past six years, the Center for Devices and Radiological Health (CDRH) has been working with multiple stakeholders to create a vision and build a foundation for the National Evaluation System for Health Technologies (NEST). One of the CDRH 2016-2017 strategic priorities is 'to establish a national medical device evaluation system with the goal of increasing access to and use of real-world evidence to support regulatory decision making and technological innovation' through building NEST. The purpose of NEST is to capture the data generated during routine patient care and to promote more efficient generation of better evidence for medical device evaluation and regulatory decision-making throughout the total product life cycle.[iii]

In addition, the Medical Device User Fee Amendments (MDUFA) IV agreement between industry and CDRH contains proposed language that includes $30 million and 10 full time equivalents (FTEs) over a five year period, to establish a Coordinating Center for NEST and conduct pilot projects to help determine the usability of real-world evidence.[iv, v] MDUFA IV requires Congressional authorization.

The NEST infrastructure central components will be populated by multiple CRNs. Each CRN will be a voluntary partnership focused on a medical condition or set of related medical conditions. These partnerships will include patient communities, government agencies, device manufacturers, institutional data partners, and methods partners.[vi] The CRNs will work towards generating higher quality evidence, more quickly, at lower costs.[vii] NEST is intended to provide infrastructure resources that expedite the generation of reliable information about medical devices to promote public health. These resources may include:

- Data from multiple sources (including electronic health records, claims, registries, patient reported outcomes, clinical trial data, etc.) connected through re-usable, standardized data use agreements (DUAs) that optimize data standardization, expedite project-specific research agreements, and reduce evidence development costs through economies of scale.

- A clearinghouse of expertise and advanced methods, tools, standards, and best practices (e.g., to detect safety events and to study clinical effectiveness of new technologies for regulatory and reimbursement decisions).

- A trusted and up-to-date compilation of reliable information on the benefits and risks of medical devices for patients and the broader health community (e.g., safety updates, recall management support, emerging effectiveness information).

The current evidence development ecosystem is composed of a range of databases, projects, and registries that are typically device, therapy or provider-focused. While many produce useful and reliable information, they generally focus on a small number of high-risk medical devices and are narrowly targeted with shorter-term outcomes. The individual activities are generally not intended to collect more broadly useful data. In many cases, their potential to reduce regulatory burdens –through routine active safety surveillance reporting remains untapped or underused. Through governance, coordination, and standardization of these activities, NEST will expand and enhance current efforts, increasing their efficiency and capabilities, and creating opportunities to generate better evidence in new areas. Examples of high priority opportunities include:

- Linking information on longitudinal outcomes, applying advanced analysis techniques, or using other best practices to expand the capabilities and improve the efficiency of registries to collect real-world evidence that may inform pre- and postmarket regulatory decisions.

- Improving the reach of innovative analytic tools, such as machine learning and the Data Extraction and Longitudinal Trend Analysis (DELTA) System for broader and more comprehensive active safety surveillance across a range of devices and data systems.[viii]

Additional opportunities include:

- Creating alternate pathways that use registry information to provide more valuable rate-based information on labeled outcomes than currently possible through individual Medical Device Reports (MDRs).

- Automating data entry and standardize outcome measures to allow evidence generation for effectiveness (including comparative effectiveness) while minimizing data collection burden.

As envisioned, NEST is a flexible, virtual system that builds on and supports existing activities that are generating evidence on medical devices. NEST may also generate evidence relevant to many other purposes, such as enhancing the quality of care and care coordination. NEST would undertake specific activities to improve safety surveillance and enable more efficient FDA decision-making. In addition, NEST would support the use by other stakeholders of the same infrastructure for their evidence development needs for FDA's premarket reviews and Centers for Medicare and Medicaid Services (CMS) decisions on payer coverage and reimbursement. NEST would identify new sources of reliable device data, and design and implement innovative ways of capturing and combining data from disparate sources while ensuring that federal patient-privacy laws, regulations, and ethical standards are followed.

Figure 1 shows an example of the NEST infrastructure and network with multiple stakeholders with a central Coordinating Center that provides governance, coordination, and standardization. The Coordinating Center will build mutually beneficial shared resources and reusable pathways with standardized DUAs.

In this section we have described components of an informatics infrastructure using NEST as an example that may provide valuable resources to the development of a variety of CRNs within health care. In the next section, we examine the DAISI CRN, which is the objective of this workshop, as a potential clinical pilot CRN to be modeled after NEST and/or utilize resources from NEST as it is being developed.

III. Clinical Pilot – DAISI CRN

Historical Summary & Current State of the Art in Treating Stroke

In 1996, the Center for Drug Evaluation and Research (CDER) approved intravenous tissue plasminogen activator (IV tPA) as the first treatment for acute ischemic stroke patients. Its use within 3 hours of stroke symptom onset improved neurological recovery and reduced the incidence of disability. Eight years later (2004), CDRH cleared the first mechanical thrombectomy device (K033736), the Concentric Medical, Inc. Merci Retriever premarket notification (510(k)). That pathway evaluated whether the Merci Retriever, in the hands of a trained interventional neuroradiologist, could be used safely to retrieve clots. The intended use of the Merci Retriever was to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke who were ineligible or who failed IV tPA therapy.[ix]

After the clearance of the Merci Retriever, additional mechanical thrombectomy devices were developed, studied in clinical trials, and cleared through the 510(k) pathway. These products are intended to revascularize the blood vessel in the neurovasculature in patients experiencing an acute ischemic stroke who were ineligible to receive IV tPA or who failed IV tPA, and the devices were to be used within 8 hours from stroke symptom onset. The primary endpoints for these studies all involved the evaluation of the Thrombolysis in Cerebral Infarction (TICI) or Thrombolysis in Myocardial Infarction (TIMI) scores. Both scores are measurements of the degree of revascularization of the blood vessel. There are currently five marketed mechanical thrombectomy devices cleared with this revascularization indications for use (IFU). In chronological order of clearance, they are:

1. Merci Retriever (Concentric Medical, Inc.; K033736)
2. Penumbra System (Penumbra, Inc.; K072718)
3. Solitaire Revascularization Device (Micro Therapeutics, Inc. d/b/a ev3 Neurovascular; K113455)
4. Trevo Retriever (Concentric Medical, Inc.; K120961)
5. Capture Revascularization Device (MindFrame,

Inc. d/b/a ev3 Neurovascular, Inc.; K141516)

Many medical devices are properly evaluated as tools to accomplish a specific task. The incremental changes in design and the criticality of deployment techniques to safety and effectiveness are key features of medical devices that make them inherently different from drugs. In some cases, registry data may support gathering evidence for the use of a device for a particular condition or patient population. Medical device regulations require the FDA to tailor the data requested from a manufacturer to address the specific safety and effectiveness questions during its premarket review.

In 2015, publications of five prospective randomized trials on marketed mechanical thrombectomy devices reported the use of Endovascular Therapy (ET) in combination with pharmacotherapy. These studies typically administered IV tPA within 3-4.5 hours from symptom onset for patients with proximal large vessel occlusion (LVO) stroke in the anterior circulation (M1 Middle Cerebral Artery (MCA) segment with or without concomitant Internal Carotid Artery (ICA) occlusion).[x, xi, xii, xiii, xiv] These studies showed superior clinical outcomes in the ET treatment arm compared to patients who only received best medical management, typically IV tPA alone. Based on this data, the American Heart Association/American Stroke Association added ET using stent-retrievers as a first-line treatment to its clinical guidelines for the early management of patients with acute ischemic stroke.[xv]

In September 2016, the FDA granted a de novo classification request (DEN150049) to allow marketing of the Concentric Medical, Inc. Trevo ProVue Retrievers based on clinical data that supported a treatment indication of:

> [T]o restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should start within 6 hours of symptom onset.

With granting this de novo classification request, FDA established a new classification regulation (21 CFR 882.5600) with product code, POL for neurovascular mechanical thrombectomy devices intended for acute ischemic stroke treatment with mandatory special controls. These special controls include performance data to demonstrate improvement in clinical outcomes of reduction in disability.

FDA also cleared the Solitaire Revascularization Device (Micro Therapeutics, Inc. d/b/a ev3 Neurovascular) for the same treatment indication after clinical and performance data that showed the Solitaire Revascularization Device was substantially equivalent to the Trevo ProVue Retrievers (K162539). Figure 2 outlines this history on a timeline.

As stakeholders in the stroke treatment field continue to innovate and improve neurothrombectomy devices, a coordinated registry may play a significant role for assessing safety and effectiveness. The DAISI CRN could ultimately accelerate bringing innovative device to U.S. physicians, and improve patient care and clinical outcome.

The Challenge in Developing Acute Ischemic Stroke Treatments

Stroke is a debilitating disease that kills nearly 130,000 Americans each year and is the fifth leading cause of death according to the Centers for Disease Control and Prevention.[xvi] Patients with acute ischemic stroke have varying background or baseline characteristics. Access to the large amounts of clinical data from electronic patient records generated during the treatment of acute ischemic stroke may support the development of personalized medicine and new diagnostic tools for this widely variable patient population. When data quality is ensured and advanced analytics are applied, data collected may also predict the potential benefits and risks and help identify early safety signals.[xvii]

Patient characteristics, such as gender, age, ethnicity, and varying co-morbidities can affect the generalizability of treatment options. Access to stroke treatments can also be impacted by many other variables. Examples of these variables, some related to clinical presentation and others not, are given below.

- Differences in time of symptom onset
- Baseline severity

- Core infarct volume and location
- Imaging criteria for patient selection for treatment
- Use with adjunct therapies such as IV tPA
- Use with other interventional devices during the surgical procedure
- Physician experience

Because there are a number of variables that can affect patient outcomes in acute ischemic stroke, the data to support currently marketed medical devices may not cover the full presentation of stroke in clinical practice. The great public health need, combined with the multiple confounding factors that may affect the generalizability of treatment for acute ischemic stroke makes it an ideal pilot model for a CRN. In the next section, we outline the characteristics of such a CRN pilot.

IV. DAISI CRN – Utilizing Existing Registries and Core Data Elements

Current Stroke Registries and Resources

A number of registries and networks currently collect data on stroke cases. These include:

- the National Institutes of Health (NIH) StrokeNet
- Paul Coverdell National Acute Stroke Registry, managed by the Center for Disease Control and Prevention (CDC)
- American Heart Association's Get With The Guidelines–Stroke database
- the Society of NeuroInterventional Surgery's NeuroVascular Quality Initiative (NVQI)

In addition, there are also various industry or hospital-owned registries aimed at obtaining quality data for systems improvement or to track device use after marketing clearance. Some of these registries have an extensive amount of patient data; however, not all currently identify the device or devices used.

At the federal level, NIH StrokeNet is an NIH-sponsored program, started in 2013 that connects a network of 25 regional centers in the U.S. It involves more than 200 hospitals, conducting small and large clinical trials and research studies to "advance acute stroke treatment, stroke prevention, and recovery and rehabilitation following a stroke."[xviii] The NIH StrokeNet is primarily intended as a network to conduct new trials and provide an educational platform for stroke physicians and clinical trial coordinators. As a registry design for clinical studies, it may not be designed to collect data on the use of marketed devices, i.e., a postmarket surveillance registry. However, other registries are intended for postmarket surveillance, such as the Paul Coverdell National Acute Stroke Registry. The Paul Coverdell National Acute Stroke Registry program, which was mandated by Congress in 2001, is intended as a collaboration of state-based registries to improve the quality of acute stroke care by measuring and tracking stroke care in hospitals and emergency medical services settings. There are currently 9 states funded by the Coverdell program.[xix] The Paul Coverdell National Acute Stroke Registry program primarily tracks clinical workflow, patient medical history,

medication usage, and medical management. However, it does not currently have any data elements for collecting device treatment evidence.

In the public domain, the American Heart Association's Get With The Guidelines-Stroke is an "[I]n-hospital program for improving stroke care by promoting consistent adherence to the latest scientific treatment guidelines."[xx] This program was initiated in 2003 and since its inception, 1,656 hospitals in the U.S. have entered more than 2 million patient records into the Get With The Guidelines–Stroke database. Among its measurable achievements, this database has led to a number of scientific publications, provided clinical tools and patient education resources, helped establish the CMS Core Stroke Measures and contributed to continuous quality improvement of numerous health care systems.

The NVQI supports hospitals and neurointerventionalists by helping them to understand best practices and outcomes of neurovascular surgery cases. Centers participating in the NVQI registry can "compare processes, complication rates, and length of stay as well as medical device effectiveness."[xxi]

Other registries owned by hospitals help track quality and performance data on acute stroke care in their hospitals, while industry-owned registries help track safety, effectiveness, or optimal use information on marketed devices.

The majority of these established registries capture a spectrum of medical care data for stroke patients during the acute in-hospital phase, i.e., until discharge or for 30 days. Longer-term data can be incorporated by linking reimbursement (CMS and private) and hospital or clinic administrative claims data to provide a more robust longitudinal data that better represents the actual health care outcomes for these patients.

The DAISI CRN is intended to achieve three goals. One goal is to identify opportunities to link all of these existing registries and data sources together. The second goal is to ensure that all of these sources collect consistent data elements. The third goal is to minimize burden, by using the infrastructure of existing registries, and adding only those core data elements necessary to meet the needs of all stakeholders. To achieve these goals, methodologies are needed to coordinate data collection and sharing between registries. Additional methodologies are needed to ensure the data can be used for the varied purposes of all stakeholders (please see Sections II and V of this paper for discussions on these topics).

Identifying Core Data Elements and Common Definitions across Existing Registries

Core data elements provide significant information about the patient care process. They are fundamental to the success of a registry network as it captures the health and disease information of all treated patients. Core data elements and standard common definitions can enable the interoperability and exchange of data between registries. Once the core data elements are established, common definitions, vocabularies, classifications, and nomenclature can be used to define each core data element.

For the regulatory decision making process and for postmarket surveillance of medical devices, the FDA has identified core data elements that we believe are relevant to collect in a nationwide registry network. To facilitate discussion, our proposed list of core data elements is given below.

- Patient Demographics (Sex, Ethnicity, Age)
- Patient Identity Fingerprint
- Name of Hospital
- Time of:
  - Symptom Onset
  - Symptom Onset to Treatment (Pharmacotherapy, ET)
  - Door Arrival to Treatment
  - Pharmacotherapy Administration to ET
  - Time from Hospital to Hospital (Transfer)
- Endovascular Treatment Used
  - Specific ET Device (Unique Device Identifier (UDI))
  - Ancillary Devices
- Concomitant Pharmacotherapy
- Number of Passes Made with Device
- Anesthesia (General, Local, None)
- Neurovascular Region Treated
- Clot Etiology
  - Size
  - Location
  - Composition
  - Density
- Patient Medical History (e.g., hypertension, other related medical conditions)

- Imaging (MRI, CT) Fields
- Symptomatic Intracranial Hemorrhage (sICH)
- Outcome Assessments (Baseline and Follow-Up Visits)
  - Modified Rankin Scale (mRS) Assessment at 90 days
  - Follow Up Intervals
  - Thrombolysis in Cerebral Infarction (TICI) Score
  - Thrombolysis in Myocardial Infarction (TIMI) Score
  - National Institutes of Health Stroke Scale (NIHSS) Score
  - Quality of Life Assessments
  - Patient Reported Outcomes
- Adverse Events (Peri-Procedural, 30 Days, 90 Days) including, but not limited to:
  - Failure to deploy device or remove clot
  - Perforation, dissection or other damage to the vessel wall
  - Vessel rupture
  - Brain edema
  - Hemorrhage, including subarachnoid hemorrhage from vessel injury
  - Hemorrhagic transformation of the treated stroke
  - Thrombus formation proximal, adjacent, or distal to the clot site
  - Death from any cause
  - Re-occlusion or stroke in other territories previously not involved
  - Partial restoration
  - Distal thrombus formation
  - Neurologic deterioration

Many of these proposed elements are included in the existing stroke registries. The creation of a CRN should not increase the burden for clinicians to input patient data into multiple registries. Instead, it should help streamline the efforts so that multiple stakeholders can benefit from information shared across the network.

V. Value of the DAISI CRN

What is Real-World Evidence?

Information and knowledge created every day as a part of routine health care or generated at home by patients using monitoring devices can be called real-world evidence. Real-world evidence collected in CRNs has the potential to benefit many stakeholders in various ways (Table 1).

Potential Benefits to Stakeholders

We envision that the value of the DAISI CRN could come from using the data gathered in it for the stakeholders as described below.

Patients can benefit from faster access to device safety and effectiveness information as well as earlier access to innovative devices as a result of streamlining the evidence generation used to support regulatory processes. This will allow patients, along with their health care providers to make informed decisions in determining their best care.

Clinicians, hospitals, and integrated health systems can use real-world evidence from the DAISI CRN for numerous purposes. Real-world evidence from the DAISI CRN may be used to develop quality data within organizations. Real-world evidence may help assess the performance of devices within their organizations. It may also help assess operator performance and support the development of clinical guidelines. The DAISI CRN may also provide relief from multiple reporting requirements. In addition, clinical data from the DAISI CRN may be used for research and scientific publications, serve as a basis for quality improvement within individual hospitals, and provide comparative performance metrics across hospitals. Information from the DAISI CRN potentially could be used for certifications such as Primary Stroke Center, Comprehensive Stroke Center, or Acute Stroke Ready Hospital. This information may also help improve local systems for stroke triage.

Regulatory agencies may be able to use data collected in the DAISI CRN to obtain additional information about the safety profile of medical devices after they enter the market. The data may also provide better understanding of device performance in different patient populations. For example, data from the DAISI CRN may be used in the postmarket surveillance of

devices to improve monitoring of adverse events and device malfunctions that occur in clinical practice. Typically, adverse effects of the device and procedure are reported when the clinician identifies a possible association to the device. However, this is not a consistent or reliable method. One goal of the DAISI CRN is to provide complete data on every stroke patient treated to allow for a more comprehensive understanding of how devices are used and how safety and effectiveness are impacted by different uses.

Device manufacturers may be able to use the data collected in the DAISI CRN to determine whether physicians are commonly using a device for an indication for use that differs from the device labeling. Data such as this may supplement or potentially serve in place of a prospectively defined clinical trial to support expanding the labeled indications for use. In addition, in certain patient populations, patient characteristics or disease presentation make it impractical to conduct a prospectively designed clinical trial, e.g., due to difficulty in obtaining sufficient enrollment. In such circumstances, data collected in the DAISI CRN may have the potential to help evaluate whether a medical device or therapy may benefit this patient population.

Payers may benefit from access to data collected in the DAISI CRN when the data can serve as high-quality evidence on device performance in clinical practice, either alone or compared with other therapies.

Clinical Evidence for Regulatory Decision-Making

The DAISI CRN may also be a source of clinical evidence to support the review of medical devices and, where appropriate, premarket decisions. The potential use of registry data to support premarket regulatory decisions and meet the needs of other stakeholders relies on including sufficient numbers of patients and collecting high-quality data at the patient level. Ideally, the DAISI CRN should capture data on every stroke patient treated in the U.S. at a consistent level of quality in each registry in the network. With adequate standards for data content, data quality, and interoperability, the information gathered from every patient can be shared among different stakeholders. These standards may also allow for growth over time that may permit valid longitudinal comparisons. Examples of scientific and clinical considerations about using DAISI CRN data to support expanded claims for marketed devices to discuss at the public workshop include:

- expanded eligibility criteria on when to use neurothrombectomy devices (e.g., times from stroke symptom onset, patient age),
- novel locations in the neurovasculature applicable to a particular device use (e.g., additional regions applicable for neurothrombectomy), and
- indications for use when medical devices are used in combination with other treatments.

Conducting Investigational Device Exemptions Studies for New Devices in a CRN

Because the infrastructure for data collection at each institution would already be established in the DAISI CRN, it may be possible for a sponsor to complete a new investigational device clinical study more quickly which may realize significant cost savings. The DAISI CRN can also provide sponsors time and cost savings by nesting clinical studies in the network. For new neurothrombectomy devices that involve new device designs, materials, or device dimensions outside of the range of dimensions for cleared devices of a similar design conducting Investigational Device Exemptions (IDE) clinical studies in the network may be appropriate. The clinical study subjects would have to sign an Informed Consent Form noting their agreement to participate in a research study. It may also be possible to conduct in the network, a randomized controlled trial that involves an investigational device and a control comparator randomly assigned to patients to provide a head-to-head comparison.

VI. Long-Term Sustainability & Business Model of the DAISI CRN

In order for the DAISI CRN to be successful, there should be a long-term sustainability plan that creates value for all stakeholders (please see discussion above in Section V and Table 1). Return on investment (ROI), cost savings, and data quality will be essential to realizing value and thus supporting sustainability. The Business Model for sustainability of the DAISI CRN may rely on the following:

- Base funding from private and public sector sources.
- NEST users pay for access to and analysis of data from participating NEST data sources.
- Long-term sustainability and growth through administrative fees for use of the system.
- A return on the financial investment, e.g., DAISI CRN and NEST demonstrated to be less expensive or more timely than standard or other alternatives.

A satisfactory ROI is critical to supporting the sustainability of DAISI CRN. Examining the ROIs of other registries, such as the Transcatheter Valve Therapeutic Registry (TVTR) may help inform the discussion of the ROI for the DAISI CRN. The TVTR is a relatively mature registry model. It was developed and is maintained by two professional societies, the American College of Cardiology and the Society of Thoracic Surgeons. It also receives financial support from a variety of stakeholders, including hospital systems, other clinical societies, and the device industry.

Cost savings is another critical element of value to support sustainability. Some potential examples of cost savings from using data from a CRN may include, but are not limited to:

- If data is utilized from the CRN to expand indications for use of marketed devices, there could be substantial cost savings compared to conducting traditional clinical trials.
- Reducing the time and cost of bringing devices to the U.S. market. For example, if the infrastructure for conducting a clinical trial is already established, study start up and conduct phases may be shortened, which could substantially reduce the length of a clinical study.
- Cost savings for embedding a clinical study in the CRN can be significant as the infrastructure for vetting and training for new clinical sites is already established.
- Continual surveillance using the CRN may detect early safety signals, and allow Corrective and Preventive Action plans to be initiated early, avoiding additional adverse events.
- New registries may not need to be developed if the data can be obtained from the CRN; therefore, saving the cost of setting up a new registry.
- CRNs may reduce the burden for clinical sites to report to multiple databases, may satisfy CMS reporting requirements[xxii] under the Medicare Access and CHIP Reauthorization Act of 2015 and FDA post-approval study requirements,[xxiii] and result in cost savings with respect to the quantity and time of FTEs needed to input the data.
- Real-world evidence of the performance of marketed medical devices may inform payers for reimbursement on the best performing devices, which may lower the research and development costs associated with a particular device or health care costs associated with clinical care and management.
- Data from the CRN may help generate or improve clinical guidelines, which may lower health care costs in general, as clinical procedures may be more effective and safe, and improve clinical outcomes and patient care. This may also realize cost savings by reducing health care costs associated with poor clinical outcomes and treating adverse events.

The quality of the data entered into the CRN is also critical to successfully realizing value of the DAISI CRN and supporting its sustainability. Methodologies need to be developed to actively monitor the quality of data entered into the DAISI CRN, and quickly

implement plans if missing data or data quality concerns are found. In addition, prior to initiating the DAISI CRN, plans should be developed based on a risk analysis of all potential scenarios where issues may arise so that mitigations can be created to address these issues.

VII. Establishment of Working Groups

Multi-stakeholder working groups for the DAISI CRN will be established in 3 areas: Clinical, Informatics, and Sustainability. The Clinical Working Group is intended to establish minimum common data elements, standard definitions, and information to be collected in Case Report Forms (CRFs). The Informatics Working Group is intended to provide guidance on the methodologies used to develop the CRN infrastructure and how the data will be collected, linked, and analyzed. The Informatics Working Group is intended to advise on efficiently embedding data collection into routine clinical workflow and participating patients' daily activities. The Sustainability Working Group will convene to discuss how the DAISI CRN will provide value for all stakeholders, assess the quality of the data collected, and long-term sustainability of the CRN. The FDA believes combining the efforts of all stakeholders will help ensure the long-term success of the DAISI CRN.

VIII. Conclusion

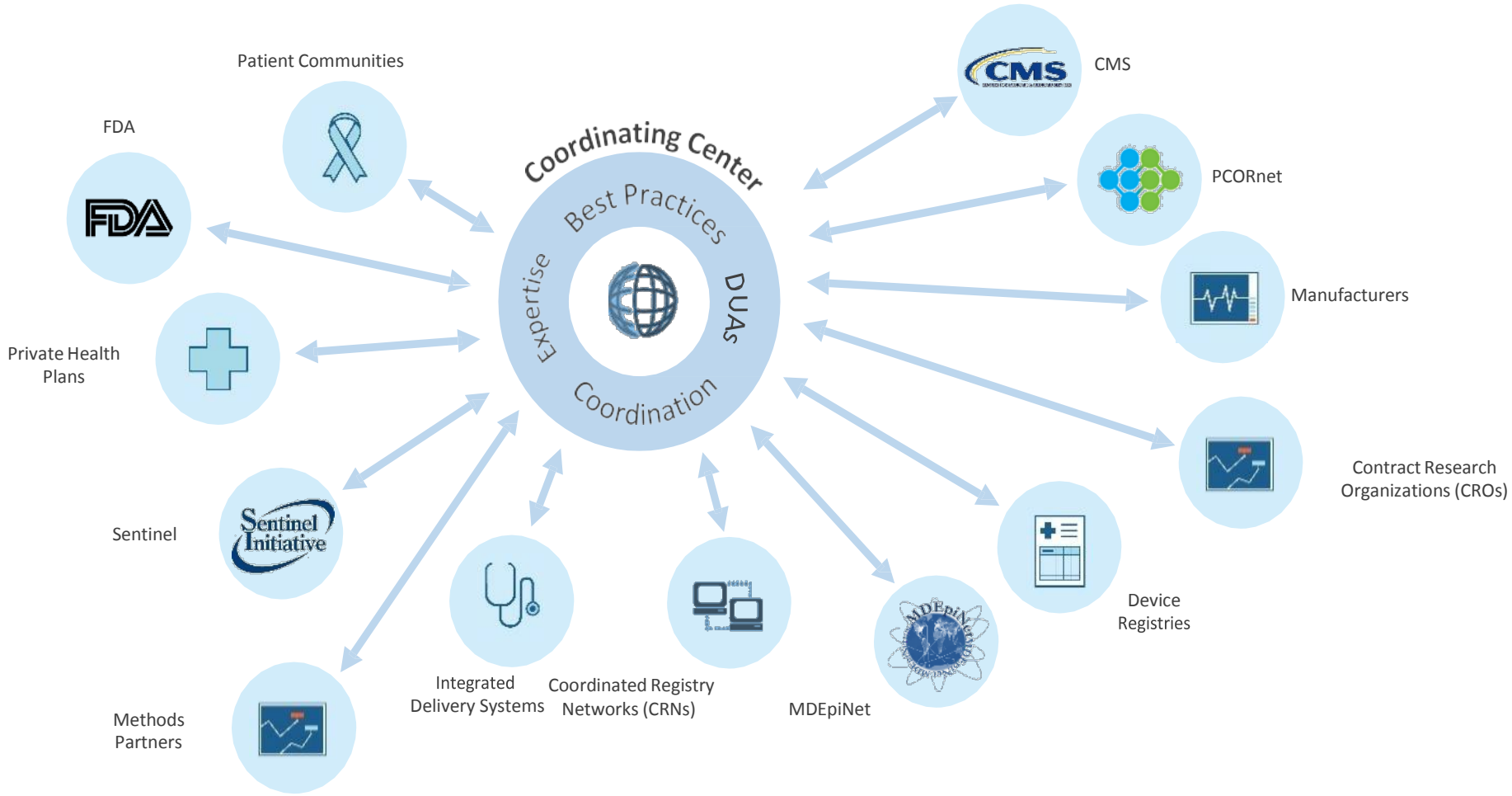
In summary, we believe the establishment of a CRN for acute ischemic stroke medical devices holds promise to advance public health. We believe it will advance the clinical care and development of innovative technologies in the U.S. for the treatment of patients experiencing an acute ischemic stroke. Multiple stakeholders may benefit from the data collected and shared in the DAISI CRN, including, device manufacturers, regulatory agencies, payers, research organizations, clinicians, hospitals, and mostly importantly, patients in the U.S. We urge all interested stakeholders to attend the public workshop on February 2, 2017 to share all perspectives on establishing a coordinated infrastructure for the DAISI CRN, including the minimum core data elements, standard definitions, and information to be collected in CRFs, and how the DAISI CRN can provide value or cost savings in the short- and long-term for all stakeholders.

IX. Submitting Public Comments

Regardless of attendance at the public workshop, if you have comments related to this topic that you wish the FDA to consider, please submit your comments to Docket Number FDA-2016-N-4187 or at http://www.regulations.gov. Instructions for submitting comments can be found at: http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm. Alternatively, you may submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852 (Please clearly identify your comments are intended for Docket ID: FDA-2016-N-4187). Both individuals and groups may submit comments.

Please note that the docket also accepts materials you may wish to include with your comments, such a references. Comments and materials submitted will be made public on www.regulations.gov, and therefore are not appropriate for addressing individual confidential medical device concerns.

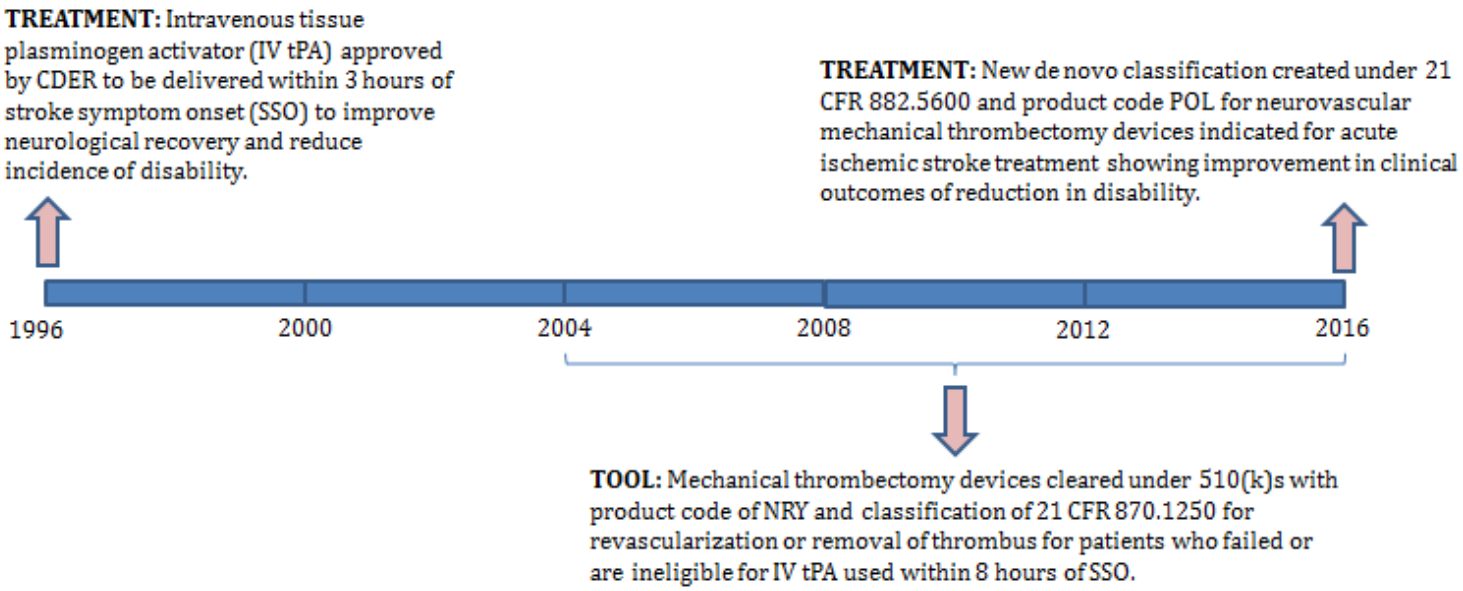
- **Figure 1. NMDES as a Coordinated Network of Partners** [xxiv]



- **Table 1. Contributions and Benefits of NEST to Patients and Other Stakeholder[xxv]**

Stakeholder	Voluntary Contributions	Benefits
Patients	• Patient engagement • Patient-generated health information o Outcomes o Quality o Adverse events • Funding from patient groups	• Safer and more effective medical devices • Faster access to trusted, personalized medical device safety and effectiveness information • Faster access to innovative medical devices as a result of streamlined evidence development and regulatory processes • Trusted, accessible source of information about devices in the news.
Clinicians and Hospitals Systems	• Routinely-generated clinical data • Discharge and care management information • Communication channels to share safety information • Content expertise • Methodology • Funding for research studies	• Safer and more effective medical devices • Faster access to medical device safety information • Faster access to innovative medical devices as a result of streamlined evidence development and regulatory processes and reimbursement processes • More timely and higher quality information on the performance of medical devices in real-world settings • Optimized device selection for specific patient cohorts • More information on medical device and operator performance • Streamlined adverse event reporting
FDA and other regulatory agencies	• Regulatory authority • Adverse event data • Content expertise • Methodology • Funding for NEST development	• Embedded NEST data collection allows more efficient compliance • Active safety surveillance for faster signal generation, refinement, and validation • Better understanding of device performance over time and in clinically diverse populations • Product tracking for recall management • Incubator for future patient safety coordinating functions
Manufacturers	• Proprietary device and registry data • Content expertise • Funding for research studies and NEST development	• Streamlined adverse event reporting • Lower cost and more efficient system for generating safety and effectiveness evidence o Support pre- and postmarket regulatory submissions o Support coverage and reimbursement decisions • Faster, less costly access to market for innovative technologies through reduced burden for pre-market data collection • Streamlined access to patient communities (including hard-to-capture subpopulations) for recruitment and engagement
Health insurance organizations	• Claims, administrative, and utilization data • Content expertise • Health economic analysis • Funding for research studies and NEST development	• More timely and relevant information on medical device performance, quality, and value • Improved ability to support higher quality and lower cost care through more timely and actionable evidence • Ability to participate in and perform more relevant comparative effectiveness research and health economic research on medical devices
Research organizations	• Content expertise • Methodology • Funding for research studies and NEST development	• More sources of standardized and high-quality data on medical devices • Longitudinal safety information on medical devices • More information on medical device and operator performance • Optimized patient selection criteria • Reduced cost and burden to conduct comparative effectiveness research and health economic research on medical devices

- **Figure 2: FDA Approved Therapies for Acute Ischemic Stroke**



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[xxiii] Postmarket requirements also include postmarket surveillance studies required under section 522 of the act as well as post-approval studies required at the time of approval of a premarket approval (PMA), humanitarian device exemption (HDE), or product development protocol (PDP) application. See http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/

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