

MedTech Strategist MARKET PATHWAYS

Global Medical Device Regulatory, Reimbursement & Policy Review

MED-EL's Maiden MDR Journey

Keeping Real-World Evidence Real

COVID Spurs New CMS Home Dialysis Incentive

Medtech Backs Bundled Payments

Medicare Mitral Valve Repair Proposal

EU IVD 10-Point Readiness Check

JULY-AUGUST 2020

MyStrategist.com/market-pathways

KEEPING MEDTECH REAL-WORLD EVIDENCE REAL

>Stephen Levin

SANDRA SIAMI

Meet Sandra Siami, the new head of NESTcc. the organization helping to drive and refine the use of real-world evidence by both regulators and industry, a trend accelerated by the COVID-19 pandemic and likely to remain when the crisis ends.

t is said that every crisis also creates opportunities. When it comes to COVID-19 and medtech, those opportunities appear largely to be taking the form of increased diagnostics applications, along with accelerating several processbased changes. Key among those is the increased use of telehealth services which has garnered much attention, but perhaps equally important is the development and growth of real-world data and evidence (RWE).

One of the biggest challenges during the pandemic for medical device companies has been conducting clinical trials given the restrictions on in-person contacts. Real-world evidence, while not taking the place of traditional clinical studies, can become an important part of that process by streamlining and reducing the time and cost of both pre- and post-market programs, thereby increasing efficiency for both industry and regulators, as well as for providers, patients, and payors. Far from being a new concept, RWE has achieved new relevance as a result of both the needs of the pandemic and the increasing development of digital health technologies and expansion of data science capabilities.

Among the leaders in furthering both the science and use of real-world evidence in medtech is the National Evaluation System for health Technology Coordinating Center (NESTcc), an organization founded in 2016 through an FDA grant to the Medical Device Innovation Consortium (MDIC), which itself is a public/private partnership that has as one of its goals to improve regulatory science by bringing together all of the key medtech stakeholders. (See "MDIC: Breaking Down Silos Across Medtech to Spur Innovation," Market Pathways, March 8, 2020.)

FDA was looking to modernize how evidence is generated for both device evaluation and postmarket safety, a task that fit squarely within MDIC's mission, resulting in the launch of NESTcc. The group's goal is to explore the feasibility of generating real-world evidence with health systems and coordinated registry and research networks through a series of what NESTcc calls Test-Cases working together with what it refers to as Network Collaborators (see Figure 1).

In her first interview since having recently been named to head the organization, Flora (Sandra) Siami, MDIC's Senior VP for NESTcc, was expansive in outlining the group's goals and the opportunities

that the current situation presents for industry and regulators to expand the use of real-world evidence, while also pointing out the challenges facing this effort. She also highlighted how these issues are critical for device companies in improving the efficiency of the regulatory process. One example is that most of the Test-Cases involve label expansion and postmarket surveillance, and NESTcc is actively exploring using RWE for other applications, including regulatory evaluations for premarket clearances and approvals. Active surveillance is also among the group's priorities, as is Unique Device Identification (UDI) technology.

Siami is also cognizant of the challenges that face any organization that brings together industry and regulators. To succeed as neutral arbiters, both NESTcc and its parent group MDIC recognize the need to be seen as relying on regulatory and data science, and not as reflecting the perspective of one side or the other. Walking that line for any group involved in the regulatory process is more important and challenging than ever before and unlikely to abate given the current political landscape. (This interview has been edited for clarity.)

>>Market Pathways: Let me start by welcoming you to NESTcc since you just joined the group on June 1, and let's begin by having you give us your background.

>>Sandra Siami: Thanks, I have 25 years of experience in medical devices and clinical trials, specifically, all on the industry side. I actually started my career doing research on an orphan device back when we didn't have the HUD [humanitarian use device] and HDE [humanitarian device exemption] pathways. There was a group of us at the American Society for Artificial Internal Organs (ASAIO) who had several devices that, in FDA's eyes, had enough information to submit for regulatory approval, but the PMA pathway was the only avenue for commercialization. And we couldn't submit because we couldn't meet the burden of those requirements.

Being into the science of medical devices, we'd go to meetings and see technologies being presented in Europe and Japan, and we'd wonder why they weren't yet in the US. The answer was because of the various regulatory pathways. Collaborating with FDA and providing input into the HDE approval pathway got me into regulatory affairs and consulting with companies in Europe and Japan on their regulatory strategy to bring devices to the US. For example, Asahi had plasma filtration devices that I helped bring to the US. The orphan device that I mentioned I initially worked on with Cleveland Clinic was produced by what was then called Pall Medical.

Then I started working at a CRO to help with their industry trials. I developed the QA and regulatory affairs departments from their infancy and led and grew a business unit that covered drugs and devices for industry. Back in the day, realworld evidence entailed bringing together manufacturers to put together a registry. My early dealings with using real-world evidence were in the AAA [abdominal aortic aneurysms] field. That involved working on the Lifeline EVAR [endovascular abdominal aortic aneurysm repair] Registry, which was a fantastic experience because it was led by the Society for Vascular Surgery and we collaborated with the FDA, CMS, NIH, clinicians, and industry participants. We had seven different manufacturers at the table to help put the registry together, define outcomes, and produce data standards. That was considered real-world evidence for us back then: using



registries, pooling data, and coming up with OPCs [objective performance criteria] or OPGs [objective performance goals] because you can't do a concurrent randomized trial for these types of devices. That has now evolved to really using so many different sources of real-world data.

•••••

Given your background and experience, what attracted you to the opportunity at NESTcc?

NESTcc was of great interest to me because the organization has been operating very collaboratively across the medical device ecosystem. Also, part of the MDUFA [Medical Device User Fee Amendments] commitment is to make sure that NESTcc is self-sustainable. Having led a business unit and been involved with clinical trials and registries, both at NERI and HealthCore, which is a subsidiary of Anthem, it was truly exciting to get in on the ground floor because I knew that how we use real-world data hasn't been tapped completely, and I knew NESTcc hadn't tapped all of its capabilities yet. We continue to evolve. In my first 30 days we launched NEST 1.0, and we have a number of initiatives planned through the rest of the year. (Editor's note: The launch of NEST 1.0 marks NESTcc's expanded capability to manage sponsor-funded research projects. Previously, the group has been leading projects funded through an FDA grant.) We have a motivated team, and while our assets at NESTcc are data environments, our real assets are our people. They're the ones who are going to make this happen for our stakeholders. We have 13 employees fully dedicated to NESTcc, not including shared services and consultants, and our plans are to double in size over the next six months.

As with any emerging field, taxonomy is important in terms of defining the discussion. Some people seem to use real-world data and real-world evidence interchangeably. Do you see them as being synonymous? If not, how do you define the two and distinguish between those concepts?

No, they're not synonymous. Real-world data is the actual data: electronic health records, claims, lab data, imaging data, patient-reported outcomes, and so on. We use that data to generate real-world evidence. To me, those are not interchangeable.

And in terms of real-world evidence, NESTcc is focusing exclusively on the medtech ecosystem, right? You're not doing anything on the pharma side.

That's right. At this time, we're not working on any pharma projects.

It would seem that prior to launching 1.0, NESTcc would have to get certain foundational systems in place, such as things

like data quality frameworks, launching active surveillance activities, and building out the legal and financial processes. What has the organization done in those areas?

With any organization, you need a solid infrastructure. You need a quality management system and standard processes and procedures, both internally and externally. A key part of this for NESTcc was the Data Quality Framework and the Methods Framework, which we published in February. These are foundational documents that we will continue to refine, modify, and build upon to define guiding principles for generating high-quality, real-world evidence. I think the initial iterations we developed with our expert subcommittee members are excellent and add to the value of NESTcc. NESTcc does have a lot of value that you can't get from just going to a CRO.

That's a good segue to discuss your view of the value NESTcc provides and to describe its business model.

Sure. We have a term in medical devices: quality by design. Pharma is now adopting it, but we've been using that term in medtech for a very, very long time. At NESTcc, we are providing quality *evidence* by design.

First, you have to build a scalable business structure. This includes our team, our processes, and our partnerships with Network Collaborators. We are in the process of expanding our Research Network to further build out the depth and breadth of data and research expertise we'll have access to for different types of studies across the life cycle, from premarket to postmarket to sunset. This is where MDIC is of great value and why NESTcc was made for MDIC, so to speak. MDIC has initiatives in science and technology, health economics, and patient value, and all of it fits with what NESTcc is doing. Incorporating all of those knowledge pieces is quite important.

The second piece that NESTcc provides as a business is ensuring transparency in terms of data provenance and traceability. The FDA is keen on using real-world data to generate realworld evidence, but the regulations haven't changed on the traceability of the data and how the data is collected. We have to be able to show regulatory grade data.

And third, because NESTcc is a neutral organization, we are a safe harbor for doing objective research. Where NEST will be utilized, at least initially, is in individual device studies, as well as class of devices studies. All of our Test-Cases are on individual devices (see Figure 2), and one Test-Case with Johnson & Johnson was featured in Market Pathways earlier this year. (See "Real-World Evidence and Johnson & Johnson: NESTcc Unlocking Doors to Medical Device Innovation and Collaboration," Market Pathways, February 19, 2020.)

What impact has the pandemic had? In certain areas of medtech, such as telehealth, COVID-19 has effectively been an accelerator, if you will, for certain trends. Has that affected NESTcc, for example in the area of data gathering? Several of the Test-Cases that the organization is working on include collection of patient-generated data from mobile devices.

I think the impact for NESTcc is a positive one because the pandemic has brought the importance of real-world evidence to light versus traditional trials and studies. Even prior to my joining NESTcc, one thing I was grappling with from leading a clinical research business unit was how we were going to continue our studies. There was a mass scramble, and telemedicine certainly helped ease data collection. People are now adopting it; using other digital technologies has certainly helped. Trials are now somewhat virtual or remote because patients couldn't or didn't want to come into the hospital, even if the researchers were still there. We had to be creative to find real-world ways of collecting data for those trials. We're not going to go back to the old normal. I think COVID-19 has changed the paradigm in terms of how we think about clinical research.

.....

Do you anticipate a lot of these changes remaining in place post-pandemic, whenever that will be?

I do. Trials that were in progress and using technologies as a stopgap might revert back to how they were originally designed. But I think as people are designing new trials, we're going to use all of the learnings gathered over the past few months, and I think digital technologies are going to stay. Telehealth is here to stay. Virtual, decentralized trials are going to stay. We have created, whether consciously or inadvertently, the learning health system that everybody has been talking about. And it's fantastic to see this change being embraced. I think it's going to stick.

.....

You bring up an interesting point, too, because as you well know, medtech is far from being a monolithic industry. Diversity is an important component. So when you talk about having a decentralized model; it seems that would be an important element for what you are doing at NESTcc, even in terms of the data staying at the institutions that are generating it and helping build this kind of medical device real-world evidence infrastructure because you're really trying to do proof-of-concept work across a wide range of uses for it to be of value both to the industry and to FDA.

Exactly. Most of our Test-Cases are label expansions or postmarket safety studies, and this goes beyond that. We're talking about OPCs and OPGs. We're talking about using digital health tools and potentially validating those measures to diversify the patient population. Clinical trials start out with very narrow populations. Once a device is commercialized, it's used in a much broader population, but its safety isn't certain. We could use more diverse populations even in the premarket stage to obtain information, even if it's supplemental information, for a regulatory application.

How does NESTcc use Test-Cases to demonstrate how generalizable the organization's data capabilities are? You're dealing with a variety of stakeholders, even within the industry, coming from different clinical specialties, in addition to FDA and healthcare systems. How do you go about establishing a certain level of trust that can engender that kind of cooperation that you need in a relatively varied ecosystem?

Part of what makes NESTcc successful is that as a neutral organization, we're able to have a collaborative and open environment to discuss certain topics. Obviously, when it comes to certain studies and actual research projects, there's a level of confidentiality for intellectual property that is not open for public consumption. Those issues still exist. But we can assess various sources to find the right data for the right types of projects at the right stage of the product life cycle: premarket, postmarket surveillance, label expansion, and so on. The use case for the evidence helps us determine what kind of data we need, whether it be for regulatory decisions, reimbursement decisions, or clinical decisions for quality improvement purposes. It also informs the study: you might have a prospective study using prospective synthetic controls, or you could be using real-world data and supplementing it with prospective data.

We don't concentrate on a specific clinical space or disease area like cardiovascular, which happens to be my area of interest and expertise. We go into other areas, including orthopedics and pediatrics. Since NESTcc cuts across disease areas, we can bring in diverse collaborators to our Research Network. That's how we are structured: we are a collaborative organization working in a collaborative community. That gives us access to the key opinion leaders and disease area experts who can come in and help drive the process.

You touched upon NESTcc's neutrality. An important issue for the credibility of any new organization is the optics– how the group is seen by the constituencies it serves. One significant issue facing medtech in a variety of forms has long been conflicts of interest between different sectors. Most prominently in this case, NESTcc is involved with facilitating close relationships between regulators and industry. How do you go about addressing that issue while preserving the group's credibility?

As a public-private partnership, MDIC obviously has established relationships across the medical device ecosystem. NESTcc's activities to date have been funded through MDUFA funding. That was a priority established by industry, but we are really

Figure 2 NESTcc Test-Cases

Test-Case	Network Collaborator(s)
Assessment of the Value of Electronic Health Records Data for Identifying Implantable Cardiac Lead Failures	STAR CRN
Characterization and Utilization of Therapeutic Cardiac Devices in Children with Congenital Heart Disease	PEDSnet
Comparative Effectiveness of Alternative Approaches for Wound Closure	PEDSnet, OneFlorida
Creation of a Patient-Facing Mobile App for a Stress Urinary Incontinence Surgery Registry	MDEpiNet
Developing Capacity to Conduct Proactive Post Marketing Safety Surveillance of Craniomaxillofacial Distractors Using Electronic Health Record Data	PEDSnet
Developing Capacity to Conduct Proactive Post Marketing Safety Surveillance of Intervertebral Body Fusion Devices Using Electronic Health Record Data	Lahey Hospital & Medical Center, PEDSnet
Developing Objective Performance Criteria (OPC) for Outcomes after Hip and Knee Replacement	MDEpiNet
Effect of Wearable Devices on Patient-Reported Outcomes and Clinical Utilization: A Randomized, Controlled Trial	Yale New Haven Hospital, Duke University Health System, Mayo Clinic
Estimating and Validating Diagnostic Cancer Biomarker IVD Test Panel Characteristics and Clinical Utility for Indeterminate Pulmonary Nodule Risk Stratification in Patients with Lung Cancer	Vanderbilt University Medical Center, Lahey Hospital & Medical Center, OneFlorida
Feasibility of Using Real-World Data to Evaluate Thermal Ablation of Liver Tumors	Duke University Health System, Vanderbilt University Medical Center, Mayo Clinic, Weill Cornell Medicine
The Feasibility of Using Real-World Data in the Evaluation of Cardiac Ablation Catheters	Mercy, Mayo Clinic, Yale New Haven Hospital
Pediatric Clinical and Health Services Outcomes following Tympanostomy Tube Insertion	PEDSnet, HealthCore
Randomized Controlled Trial Examining Real-World Effectiveness of a Prescription Digital Therapeutic for the Treatment of Insomnia and Depression	Yale New Haven Hospital, Mayo Clinic
Real-World Clinical Outcomes in Patients with Mechanical Heart Valve Replacement and Anticoagulation Variability	Vanderbilt University Medical Center, Weill Cornell Medicine
Real-World Evidence Analysis for Pre-Market and Post-Approval Studies of Annular Closure Device	HealthCore
Structured interviews of Lived ExperiencE in Patients (SLEEP study) Obstructive Sleep Apnea and Central Sleep Apnea	HealthCore, PEDSnet
Synthetic Mid-Urethral Slings for Stress Urinary Incontinence in Women	Vanderbilt University Medical Center, Lahey Hospital & Medical Center, Mayo Clinic, Weill Cornell Medicine (MDEpiNet), Yale New Haven Hospital
Testing the Feasibility of Registry and Claims Data Linkages	HealthCore, Mayo Clinic
Testing the Use of Real-World Data from Three Unique Sources to Expand Indications	MDEpiNet, Duke University Health System, OneFlorida
Use of Real-World Evidence to Characterize Patients with Uncontrolled Hypertension	Yale New Haven Hospital, OneFlorida

an FDA initiative. The result is the kind of collaboration where we're able to come and talk together on neutral territory. It's also important to note that participation in NESTcc doesn't guarantee approval of a regulatory submission; the data has to show and meet the FDA criteria for approval. But what we can do within NESTcc is ensure that the appropriate types of data are used and that the results generated have been validated within our quality and methods frameworks.

The vision that you have presented for NESTcc is quite expansive. In establishing a pathway with specific priorities, how do you guard against outsized expectations when you're managing such a broad portfolio and dealing with a huge range of stakeholders and clinical areas?

.....

One of the things I've been working on with our NESTcc team is our business plan. As with any organization, we identify priorities, and as with any organization, when a pandemic hits, we have to re-prioritize our plan. So I anticipate adapting to meet needs as they arise and pivot appropriately. We're nimble enough that we're able to do that. We also have a fantastic Governing Committee, which is an immensely helpful advisory group.

Let me give you an example of a recent pivot on the MDIC side. MDIC has been working on a diagnostic accelerator program. What better collaboration for NESTcc to participate in than to be able to move forward appropriate diagnostics through the accelerator program, using the environment and ecosystem we've created? Being able to adapt like that is going to be important. Being tied to an unyielding business plan isn't what will make NESTcc successful over the next five or 10 years. We need to have both short- and long-term priorities in that plan to enable us to adapt to whatever changes arise, and COVID-19 is an extreme such example.

Let's talk about a couple of areas in which NESTcc has launched Test-Cases. My understanding is that one of the important issues the group is working on is the extent to which industry can extract unique device identification information from products. Some people see the fact that there is no UDI system in electronic health records, for example, as a barrier in the device space, in contrast with pharma because obviously devices have different components, which raises its own challenges. How are you approaching that issue?

We do have an UDI assessment that we have been working on with various collaborators. Certainly, with the use of electronic health records, we can access identifiers that might have the lot number and the type of device. We can compare that to industry data of where they've sold which device, and who has what stock. So it can be done. It's more work without the UDI, but our Network Collaborators have worked together to create and validate datasets. I'm very excited about this project because this was one of the first things I thought about, even when NESTcc was first being developed back in 2016. I think we have come a long way since then. People not just within industry, but the multiple stakeholders that we have within the organization have become aware of the issue and we're now trying to solve for that to make it more effective because it will be a win for everybody.

We talked earlier about telehealth. Let's expand to focus on digital health, broadly speaking. NESTcc was cited in the FDA's digital health software precertification program as potentially being able to provide the kind of real-world evidence and data necessary for these kinds of projects to succeed. How is NESTcc looking to incorporate technologies like AI and machine learning into medtech software? Because there are still those in the industry who would prefer to focus on more traditional medical device constructs.

We have several potential proposals that are looking at software as a medical device, including algorithm development using machine learning. And of course, AI opens up a new area of possibilities for what we can do with real-world data. It's certainly on the horizon and we are expanding our Governing Committee to include digital health representatives because that is an important, growing area, and NESTcc needs to be at the forefront. We need to be proactive and not reactive in order to be successful.

.....

It would also seem, when talking about AI and extending that into big data, that there is a significant potential opportunity in using real-world data for regulatory bodies, starting with FDA, but also for other regulatory bodies. Is that an increasing area of regulatory interest and one that NESTcc is exploring?

Certainly, FDA has mentioned it several times. You'll see that in guidance documents and in releases of programs initiated regarding real-world data. I also see that type of adoption in Europe, which is why it's important for NESTcc to have research collaborators globally. I see that becoming a reality very soon, and I do think that will be adopted more globally by many regulators, not just FDA.

I noted that NESTcc, like MDIC, has a variety of constituencies, and we've talked about industry, regulators, and the variety of clinical specialties; I would be remiss if I didn't ask you about patients and the role of patient advocacy organizations, which is among the priorities for MDIC. How do patients fit within your group's ecosystem?

It is immensely important that we include patients, especially now. That means not just having patient advocacy groups, but making sure that we are including patients in the design process and empowering patients in decision making around their devices. Patient advocacy representatives are key voices on the NESTcc Governing Committee, and we actively seek public input on our initiatives to help inform and sustain a patientcentric approach. The patient perspective is definitely a huge part of clinical trials, not just for us, but for all clinical trials and all data that's going to be collected for regulatory decisions. Ultimately, we want to support decision-making and improve the health outcomes of people using medical devices.

••••••

Looking ahead, another important emerging issue is potentially using NESTcc infrastructure for active surveillance. For example, if the FDA had a particular safety question about a specific device or group of products, do you see your organization being able to become a source of data for the agency? One recent such potential example that comes to mind, obviously this is before you came on board, was the issue of mortality signals that were tied to paclitaxel-coated cardiovascular devices.

You're right, that was before my time at NESTcc. When that issue first came up, I thought that it was what NESTcc could and should be used for. I was involved in an NIH-funded study for lower extremities during that time, and that had a huge impact on our trial. We lived, ate, and breathed it to be able to get the right data. What ended up happening was individual industry participants did their own studies and re-studies, and there were a couple of societies that got together to look more closely at a registry. But we need to think bigger. Unfortunately, NESTcc was not at a stage at that point to have jumped in. But that would have been a fantastic case for NESTcc to have executed and been successful. When I talk about doing studies as a device class, NESTcc could definitely do a class kind of analysis with our Network Collaborators.

The same is true for another example. Previously I was part of the Preserve IVC (inferior vena cava) filter trial, where we had multiple manufacturers participating to use IVC filters instead of having a 522 [postmarket surveillance] study mandate. But participating in Preserve, we found out more long-term information—up to two years—about how the device was doing, at what points were they being retrieved, and other safety information on the device. But because we also had a larger aggregate pool with each manufacturer having 300 patients, and using the pool as a class, we could have—potentially if the data were positive—been able to use it for a labeling expansion for the participating manufacturers. In my mind, that's where the low-hanging fruit is for NESTcc.

Along those lines, is one of the goals, for example, to use larger electronic data sets to look for potential associations

of risk with devices, particularly those that are new and unanticipated? In that way, NESTcc potentially could provide FDA with signal identification and verification, and determine if the risk is valid or maybe it's unrelated to the device.

Exactly. The active surveillance piece is interesting because it is similar to the FDA Sentinel system that pharma has. The intent of active surveillance is not to be a "gotcha." You can identify trends or new UADEs (unanticipated adverse device effects) that you couldn't have identified or been able to predict in the smaller studies that are typically done in devices during the trial phases. Doing more types of studies within the active surveillance environment is an exciting piece that we're just kicking off. We've assembled an Active Surveillance Task Force with patients, clinicians, health systems, FDA, payors, and the medical device industry, and we are in the process of building a cloud platform for active surveillance studies.

.....

You have spent 25 years in the medtech industry, much of that working with regulators, so you know all too well how tradition-bound both of those groups can be regarding how data has been collected for clinical trials and used to regulate devices. We have been talking about NESTcc taking on a number of new approaches, some forced by the pandemic and others driven by efficiency. NESTcc was launched under the aegis of FDA, but what kind of reaction has the group received from both regulators and industry? Does it feel as if you're pushing the boulder up the hill, or are people generally ready to adopt these new approaches, perhaps somewhat forced by the pandemic? I know that you've only been with the group for a short time, but I'm guessing this is a topic that you've previously discussed with peers and stakeholders.

Yes, absolutely, and I think it depends. People are receptive to using real-world data for certain types of studies-primarily post-market. We certainly had larger companies participating in those, although I do think that from a risk perspective, larger companies tend to be more risk averse, just by their nature. But the use of real-world data in a non-traditional way or premarket, let's say, hasn't quite been adopted as broadly yet. I think people like the idea because we've been talking about it for years and it's now coming true. It's just coming to fruition, and I think a lot of people are in a wait-and-see mode. That's why our public forum [the NESTcc Forum, scheduled for September 22, 2020] is going to be important for industry because they want to see the results of the Test-Cases. Others are going to be able to take risks and be at the forefront. Some large companies will lead the way as trailblazers, but most of it I see coming from the smaller, mid-sized companies. Again, I think people have embraced the idea of real-world data, but not for all types of studies throughout the life cycle of the product just yet. That's what we're now working on expanding and proving.