U.S. Clinical Trial Data Announced on Wearable Artificial Kidney Prototype

The field of nephrology has seen little in the way of dialysis innovation for patients with end-stage renal disease (ESRD). One nephrologist has been working for more than a decade to develop a wearable, continuous hemodialysis device to improve outcomes and quality of life for patients with ESRD. The Wearable Artificial Kidney (WAK) was named one of three potential ESRD device innovations in the U.S. Food and Drug Administration’s (FDA) Innovation Pathway 2.0 program. More recently, on November 2, 2015, it was accepted in FDA’s Expedited Access Pathway (EAP) program. Victor Gura, MD, founder of Blood Purification Technologies, Inc. (Beverly Hills, CA, USA), presented the first U.S. clinical trial data on the WAK at the American Society of Nephrology (ASN) Kidney Week 2015 conference, held November 3-8, in San Diego, CA, USA. He spoke with Health Technology Trends about the findings, his work with FDA, and the need for funds to get a smaller, more efficient device to market.

An Unmet Need

“When you do hemodialysis with the current devices . . . basically you filter a patient’s blood for three or four hours” three times a week, explained Gura. Patients treated in dialysis units in hospitals or standalone dialysis centers are “tethered” to a device as blood is removed from a surgically created vascular access point in the arm or through indwelling dual-lumen catheters placed in a central vein. Aside from the inconvenience this regimen imposes on patients, “the outcomes from dialysis are not very good,” said Gura. “Quality of life is not very good, people get sick a lot, have a lot of heart disease, hypertension, stroke, and they go to the hospital a lot. We also have an unacceptably high mortality rate.”

Continuous Dialysis

Gura said he and his research partners noticed that patients in a few places around the globe had half the mortality rate of patients in the United States. “We found that in places where outcomes are far superior in terms of complications, quality of life, and mortality, that patients dialyzed not three or four hours, but seven or eight, so time on dialysis is a big deal.” In cases in which people dialyzed every day, he said, “wonderful things happened. Patients felt stronger, they had an appetite, they could eat everything.”

But changing clinical practice to daily hemodialysis isn’t practical, said Gura. “Patients who are on dialysis three times a week don’t even want to hear of sitting on the machine for longer periods of time. They want to have a life.” Nor is there incentive for dialysis centers to accommodate longer dialysis sessions given the limited number of dialyzers in a center. “That requires the investment of capital that [providers] can’t afford to make,” and payers don’t want to pay for it, he added.

Gura and colleagues developed the WAK to be wearable—eliminating the need for electricity or a water supply—and continuous. The technology is a dialyzer that filters waste and
removes extra fluid from the blood, consisting of a tool belt that holds two 9 V batteries, a filter, and a 375 mL dialysate cartridge. The patient is connected via a catheter to the continuously running system.

Unlike a traditional hemodialysis unit that uses 40-plus gallons of water per treatment, Gura’s devices uses 400 cc of water and chemicals that were originally developed for NASA’s Apollo mission to the moon, intended to clean urine so astronauts could drink it. Not surprisingly, the idea wasn’t widely accepted but was used in dialysis machines in areas where water was in short supply, such as military and field hospitals. “I figured I could use the same chemicals that would basically purify the water and recirculate it, so I used the same chemicals that were supposed to go to the moon,” said Gura.

Human Clinical Trials

The first WAK trial took place in Vicenza, Italy, with six patients who wore the WAK for six hours, according to Gura. The trial in London, UK, had eight patients who wore the WAK for four to eight hours. Researchers at the University of Washington (Seattle, WA, USA), led by Jonathan Himmelfarb, MD, enrolled 7 patients who were to wear the device for 24 hours. All patients remained hemodynamically stable with no serious adverse events. Serum electrolytes and hemoglobin were stable, and fluid removal was consistent with prescribed ultrafiltration rates, according to the data. Mean blood flow rate was 42 ±24 ml/min, and dialysate flow rate was 43 ±20 ml/min with no laboratory evidence of hemolysis. Mean blood urea nitrogen, creatinine, and phosphorus clearances were 21 ±13, 20 ±11, and 22 ±12 ml/min, respectively, during the first hour of treatment.

“We removed all the salts, all the toxins we need to remove [at] more or less the same rate as the kidneys would do,” said Gura.

Treatment was stopped after 4 hours due to clotting in 1 patient, and treatment was stopped after 10 hours due to “discoloration of dialysate.” Gura said they encountered some “expected technical difficulties,” such as excessive CO₂ bubbles in the dialysate, variable blood and dialysate flow rates, and tubing leaks during the priming phase.

“These problems were exactly what were [described] in the Lancet [2007 Dec 15;370(9604):2005–2010], so we do know we need to redesign and manufacture a few pieces,” Gura said. “FDA said, ‘we want you to use the same machine you used in London in Seattle,’” he said of the U.S. clinical trial; thus, “we reproduced in Seattle not only the good things that happened in London, but also the bad things” that he knew needed correcting.

The London study enrolled eight patients. Clotting of the vascular access occurred in two patients when the dose of heparin was decreased and the partial thromboplastin time returned toward the normal reference range in both patients. The fistula needle became dislodged in one patient, but safety mechanisms prevented blood loss. The needle was replaced and treatment continued.

Gura said trial patients were encouraged to eat and drink while wearing the device. Patients on dialysis typically follow diets that restrict foods high in salt, potassium, or phosphorus. Gura said patients consumed pretzels, mashed potatoes, bananas, macaroni and cheese, pizza, and orange juice without increasing levels of sodium, potassium, or phosphorus. Patients did not take phosphorus binders during treatment, which is another common requirement of patients on dialysis.
Catheter infection risk is one safety concern that has not been studied because of the short clinical observation periods. “We have mitigation technology to mitigate the risk of clotting and infection,” Gura said. “I can’t assure you 100% we can prevent infection or clotting, but we’ll be pretty successful.”

Gura is quick to point out that the current iteration of the WAK, a tool belt carrying roughly 10 pounds of equipment, is not the device he intends to reach the market. “We’re going to improve the technology,” he said, adding that he would like to cut its weight by half.

**FDA’s EAP Efforts**

According to FDA, the Innovation Challenge and IP 2.0 program for ESRD devices successfully concluded in November 2014. Three participating developers reported that the program established an environment of trust that stimulated technical enhancements and significantly shortened their devices’ pathway to market.

Now with EAP designation for the WAK, “we’ve had very intense and constructive discussions about when and how we’re going to do the next trial,” said Gura, who added that FDA has “given me an enormous amount of guidance and support, and they have spared no effort to make this successful,” he said.

For the next phase, Gura said his team and FDA are discussing adaptive trial design, use of Bayesian statistics, and postmarket studies—all factors “that will have an impact on the number of patients FDA will require and the length of the trial,” he said. FDA is also emphasizing patient preference, according to Gura. In May 2015, FDA issued draft guidance for manufacturers on including patient preference data in Premarket Approval applications, Humanitarian Device Exemption applications, and de novo classification requests.

“Patient preference is important,” said Gura. “It’s about the patient. I get questions from patients like, ‘Can I go and play tennis with [the WAK]?’ The answer is yes.” On the other hand, he said, “I have a patient that said, ‘I don’t want to wear this device [as I repel down from a high mountain on a rope, and I don’t think a football player could play football wearing your device,’” Gura said. “But I don’t think most dialysis patients are repelling from a high mountain, and [most don’t] play football,” he remarked. In some cases, “they would be happy to move from the gurney to the chair.”

Financing is Gura’s biggest hurdle. “We’re only as good as the money we have to do this,” he said. “Now that we’ve proven the concept it’s time to get serious with serious money, and we will do that.”

**Other Solutions under Development**

Some serious money has come to investigators developing a bioartificial kidney. Researchers at the University of California San Francisco (UCSF, USA) and Vanderbilt University Medical Center (Nashville, TN, USA) announced a $6 million grant from the National Institute of Biomedical Imaging and Bioengineering’s Quantum Program to support development of nanofilter technology to be incorporated into an implantable artificial kidney device. The device is based on semiconductor fabrication techniques developed for the microelectronics industry. The bioartificial kidney weds filters made of silicon with living human kidney cells cultured in the lab from samples harvested from deceased donors. In September 2015, the project received EAP designation from FDA. Researchers presented on the state of the project at ASN Kidney Week 2015. “We aim to conduct clinical trials on an implantable, engineered organ in this decade, and we are coordinating our efforts with both the NIH [U.S. National Institutes of Health] and the [FDA],” said Shuvo Roy, PhD, a UCSF bioengineer who led the research with Vanderbilt University nephrologist William Fissell IV, MD.
The Road to Health IT Interoperability May Be Paved with Apps

The rallying cry for interoperability is familiar to those following, if not working in, health information technology (IT). Researchers from the U.S. government-funded Substitutable Medical Applications, Reusable Technologies (SMART) project are proposing healthcare-specific app standards available in an open-architecture platform that could foster innovation, allowing clinicians access to clinical-decision-support tools, population health apps, real-time epidemic alerts, and genomic data from apps that “bi-directionally connect delivery system data to mobile apps.”

David Kreda, an independent consultant who works with SMART researchers, discussed the app work, as well as a recent paper published by SMART leaders that frames the vision of an “apps-based information economy.” Kreda spoke at the 8th Annual Mid-Atlantic Healthcare Informatics Symposium, held October 23, 2015, in Philadelphia, PA, USA.

Interoperability Mantra

The meaningful use program created by the Health Information Technology for Economic and Clinical Health Act of 2009 can claim responsibility for 96.9% of U.S. acute nonfederal hospitals using EHRs, according to the latest data from the Office of the National Coordinator (ONC) for Health IT. In January 2015, ONC released a 10-year roadmap to interoperability with a goal that the “majority of individuals and providers across the care continuum [will be able] to send, receive, find and use a common set of electronic clinical information at the nationwide level by the end of 2017.”

Some stakeholders have criticized ONC for neglecting to impose interoperability standards in EHR certification, allowing for silos of health data in systems that can’t exchange information. Proprietary vendor software and regional competition among hospitals are barriers to interoperability. Providers and vendors both cited a lack of standards and no national patient identifier as interoperability roadblocks, according to a recent College of Healthcare Information Management Executives report.

SMART Work

SMART is an advanced research project started with a four-year, $15 million contract with ONC. Its overarching goal is “identifying standards and formulating them for use in clinical systems,” according to Kreda. SMART’s leadership team draws heavily from Harvard Medical School/Boston Children’s Hospital (Boston, MA, USA), and the advisory committee is a mix of professional societies, health systems, industry, and healthcare services companies, according to the website.

The goal of designing the “app store for health” is part of the SMART Platforms initiative led by Kenneth D. Mandl, MD, MPH, professor of biomedical informatics and pediatrics at Boston Children’s Hospital. Mandl and colleagues authored a paper in Cell that describes how standard, open software interfaces could lead to the development of apps that foster data-sharing across physicians, health systems, translational researchers, and patients (2015 Jun[Epub ahead of print]).

“You’re tools are stunted,” Kreda said of the current EHR systems that clinicians use, requiring users to click through multiple screens to access data. Also problematic is the lack of customization for specialists; a dermatologist and a gynecologist share the same EHR experience, unless specialists purchase custom software that can’t be properly integrated across delivery systems.

Citing the Cell paper, Kreda described a framework for application programming interfaces (APIs)-enabled EHRs. Within this framework, the end user selects apps “from a gallery or app store” the way smartphone users select apps. In this framework, EHRs can be “widely connected to modern day software applications running on the web, local intranets, or mobile devices,” wrote Mandl in the paper.

“Because no one solution will fit all, an ecosystem of diverse apps will make it easier to experiment with a far wider range of patient management options.”
Because the apps are written using standard API for healthcare data, clinicians’ app selections aren’t limited by their EHR—provided the EHR software is API-enabled.

EHR Vendors, Third-party Apps

Kreda said that vendors are beginning to warm to the idea of third-party apps. EHR vendor Epic, Inc. (Verona, WI, USA) announced it would support an apps exchange for developers.

Attendees at the 2014 Healthcare Information and Management Systems Society Conference, held February 23-27, in Orlando, FL, USA, may have seen the demo of apps developed using Fast Health Interoperability Resources (FHIR®) standards that allowed retrieval of patient data from the Millennium® system (Cerner Corp., Kansas City, MO, USA) and VistA, the Veterans Health Administration EHR system. Kreda said a pediatric growth chart app developed by Joshua C. Mandel, MD, SB, at Boston Children’s Hospital with Fjord, the design and innovation unit of Accenture (Chicago, IL, USA), “will soon go live with two major EHR vendors.”

Mandl and colleagues urged physicians, practices, and larger healthcare delivery organizations that are purchasing or renewing health IT contracts to “adopt common RFP [request for proposal] language specifying and requiring inclusion of a uniform healthcare API” in contracts. Mandl recommends SMART API based on open standards, including Health Level 7’s FHIR (see sidebar on page 4).

SMART Vision

In the “app store for health,” these apps will give “new life” to data in the EHRs and other health IT platforms, allowing users to “visualize risk, trends, and trajectories; mash up clinical records with external data sources; and deliver decision support to clinicians and patients during and between encounters,” according to Mandl. In addition, new sources of data from sensors, devices, and patient reports can be integrated in the record, which will “change the experience of physicians and patients,” Mandl predicted.

Apps can also incorporate linking of genomic data and further the precision medicine initiative announced by President Obama, according to Mandl, a bold initiative that requires “data collection, discovery, and analysis.”

Overall, “because no one solution will fit all, an ecosystem of diverse apps will make it easier to experiment with a far wider range of patient management options,” wrote Mandl.

This “modular plug and play” format is a “new form of interoperability” that is not without new concerns such as a need for “standards for handling data privacy and security” that the Health Insurance Portability and Accountability Act doesn’t address. Business Associate Agreements may be needed between app developers and clinical entities. And some EHR vendors may need to “retool their products” to become more nimble and provide “sub-second response time.”

The apps themselves will need to be vetted, but it’s unclear how and by whom, given the U.S. Food and Drug Administration’s position to stay at an arm’s length from mobile health apps. Another uncertainty is “how large the ecosystem of apps will have to be for a physician to access all the necessary data” on a patient, considered Robert P. Maliff, director of ECRI Institute’s Applied Solutions. He noted that current apps deal with very specific data sets. “Will a physician have to have 100 of these apps in order to get all of the information necessary” to treat a patient?

WEARABLES DATA IN THE EHR? NOT SO FAST

Some in healthcare informatics consider sensor data from wearables a potential data tsunami. The visionaries in this field have high expectations for the incorporation of activity, sleep, and vital signs data into the electronic health record (EHR). While not hard to conceptualize, it may take some time for seamless data access and meaningful integration of sensor data in EHRs, according to Kenneth D. Mandl, MD, Boston Children’s Hospital (Boston, MA, USA).

“The reality of the growth in the ‘wearables’ industry (Fitbit or Apple Watch) has vastly outstripped any standardization efforts, which suggests that the initial sets of apps for these data streams will remain confined to their respective platforms and also integrate with EHR data in very limited ways,” Mandl and colleagues stated (Cell. 2015 Jun[Epub ahead of print]). So-called “cross-platform standardization” may require “patient-driven open data efforts.”

Additional questions, such as who will pay for the apps and who vets and regulates them, are issues the industry will need to consider as technologies advance and integration becomes possible.
CMS Announces Final Rule on Hip and Knee Bundled Payment Pilot Program

Hospitals required to participate in Medicare’s bundled payment pilot project for hips and knees have a little more time to prepare. The U.S. Centers for Medicare & Medicaid Services (CMS) issued a final rule on its Comprehensive Care for Joint Replacement (CJR) pilot project. The mandatory program will affect hospitals in 67 regions across the United States that will be paid in bundled payments for hip and knee replacement procedures in a pay-for-performance model complete with incentives and penalties. The final rule includes several concessions to the proposal, one of which is a later start date of April 1, 2016, instead of January 1 (see “Medicare’s Bundled Payment Joint Replacement Program Puts Hospitals in the Driver’s Seat” Health Technology Trends 2015 Sept;27[9]:7-8).

Overview of the Plan

The CJR project involves a pay-for-performance methodology in which quality measures—a complications measure and a patient experience survey measure—are calculated at the end of the episode of care. The procedures include a lower-extremity joint replacement or reattachment, specifically Medicare Severity-Diagnosis-related Group (MS-DRG) 469 (major joint replacement or reattachment of lower extremity with major complications or comorbidities) and MS-DRG 470 (lower-extremity replacement/reattachment without major complications or comorbidities).

The episode of care includes the procedure, the inpatient stay, and all related care covered under Medicare Parts A and B 90 days after discharge (i.e., hospital care, post-acute care, physician services).

Participants are paid in the usual fee-for-service model, and a reconciliation takes place at the end of the calendar year.

A “target payment” for the episode of care is calculated based on a beneficiary’s fracture status and other quality and risk calculations and is reconciled against actual reimbursed fees for the episode of care.

If the target payment is higher, the hospital is entitled to a “reconciliation payment,” but if the target payment is lower, the hospital must make a “Medicare repayment.”

Hospitals won’t be responsible for the repayment in the first year but will be responsible for repayments at the end of years two through five.

Participants will also have access to claims data and educational resources to better understand lower-extremity joint replacement patients’ post-acute care needs and associated spending.

CMS said performance measures will be publicly reported on the Hospital Compare website.

Concessions

CMS received more than 400 comments on the proposed pilot issued on July 9, 2015. The American Academy of Orthopedic Surgeons (AAOS) issued a letter to CMS requesting a one-year extension for the program. The American Hospital Association requested a six-month delay.

The revised time frame for the CJR pilot runs April 1, 2016, through December 31, 2020. CMS also adjusted the number of participating hospitals and geographic locations to 67 from 75, due in part to some hospitals’ lower procedure rates or participation in other payment models such as the Bundled Payments for Care Improvement (BPCI).

Other changes to the proposal include a revision of the composite quality score methodology with a more gradual transition to downside risk. Hospitals won’t be responsible to pay CMS back at the end of the first year and will have “stop-loss limits” of 5%, 10%, and 20% at the end of years two, three, and four and five, respectively. CMS also established a parallel approach to limit the reconciliation payments to hospitals.

AAOS acknowledged CMS’s revisions to the pilot in a press release, but voiced concern over the “absence of risk-adjustment in the program and a lack of designated
physician leadership for episodes-of-care.” In the CJR pilot, the onus is on hospitals to coordinate postacute care with primary care providers, home health agencies, and skilled nursing facilities.

Reducing Variation in Quality, Cost

CMS said CJR and other pilots aim to address the wide range in joint replacement costs, which can run from $16,500 to $33,000. CMS said it based CJR on previous experience in paying for orthopedic services in the Medicare Acute Care Episode (ACE) demonstration initiated by the Center for Medicare & Medicaid Innovation (CMMI). The agency reported an average gross savings of $585 per episode for a total of $7.3 million across all episodes (12,501 episodes or 3.1% of the total expected costs for these episodes). After accounting for increased postacute care costs that were observed at two sites, Medicare saved approximately $4 million, or 1.72% of the total expected Medicare spending.

Another initiative, BPCI, is still ongoing. ACE and BPCI are voluntary; however, CJR is the first CMMI model that requires participation of select acute care hospitals.

CMS said it expects to save $343 million over the five performance years of the CJR model.
In the interim, other attempts to develop a wearable peritoneal* dialysis system seem to have stalled. For example, AWAK Technologies Pte Ltd. (Singapore/Burbank CA, USA) had this goal on the horizon; however, the latest news from the company is related to partnerships with entities to develop a portable nighttime dialysis machine. Fresenius SE & Co. KGaA (Bad Homburg, Germany) also had plans to develop a wearable peritoneal device, but no details are available on a prototype.

No data are available beyond animal studies on the wearable artificial kidney under development through the Nephron Plus Project. The project is funded by the European Union, and clinical trials were slated for 2014.

* The WAK is designed to perform hemodialysis, as opposed to peritoneal dialysis, in which the peritoneal membrane and dialysate is used to remove wastes and extra fluid from the body. This can be done by continuous ambulatory peritoneal dialysis or automated peritoneal dialysis, according to the National Kidney Foundation.