

## Strengthening the Evidence Base for Pediatric Medical Devices Using Real-World Data

Rachael L. Fleurence, PhD<sup>1</sup>, Christopher B. Forrest, MD, PhD<sup>2</sup>, and Jeffrey Shuren, MD, JD<sup>3</sup>

In 2018, the US Food and Drug Administration (FDA) approved a 15-mm rotatable mechanical heart valve, the smallest device of that type, that allows cardiac surgeons to treat newborns and infants in need of a mitral or aortic valve replacement. Until then, only larger sized valves were available and were often not suitable for the smaller size of children's hearts. The device was approved based on the results of a single-arm study of 20 pediatric patients with serious heart failure ranging in age from 1.5 weeks to 27.0 months at the time of mitral valve implant.<sup>1</sup> However, the vast majority of medical devices are not tailored to children, and adult versions are used off-label with little to no evidence for their use in children. Knowledge about device usefulness, effectiveness, and safety is largely based on the collective experiences of pediatric clinicians and hand-me-down evidence from studies in adults.

Medical devices are regulated in the US by the FDA, primarily by its Center for Devices and Radiological Health. For premarket approval, each device reviewed by the FDA must demonstrate a reasonable assurance of safety and efficacy based on valid scientific evidence to obtain marketing authorization. The range of diagnostic and therapeutic device types is vast, from treatment of such conditions as bone fractures (with screws and plates), heart conditions (mechanical heart valves, defibrillators, pacemakers, stents), diabetes (artificial pancreas, continuous glucose monitors), hearing loss (cochlear implants), and chronic otitis media (tympanostomy tubes).

Despite regulatory and legislative changes that have sought to encourage the development of medical devices for pediatric patients, only a small number of devices are submitted to the FDA each year for a pediatric indication.<sup>2</sup> A review of pediatric device approvals found that most high-risk pediatric devices are initially approved on the basis of trials in patients 18 years and older, with indications for use generally limited to these older youths.<sup>3</sup> As a result, most devices in pediatrics are used off-label, with or without modifications by physicians to tailor them to the size and needs of their pediatric patients, a strategy supported by the American Academy of Pediatrics, which recognizes that this may be the only way to provide certain treatment options to infants, children, and youth.<sup>4</sup> On the economic front, financial incentives are lacking for manufacturers to develop medical devices and to conduct research specifically for

pediatric populations owing to reimbursement challenges and limited interest by investors.

Clinical evidence, whether it is intended for regulatory or clinical decision-making purposes, should ideally reflect the spectrum of pediatric patients, defined by developmental differences in physiology, growth, and behavior, as well as age-dependent changes in metabolic and hormonal activity levels. These factors can impact the performance of a medical device and its associated clinical outcomes.<sup>5</sup> For example, clinical outcomes associated with a cardiovascular device can be influenced by heart rate, blood pressure, and pulmonary and systemic vascular resistance, as well as the size of the heart and vasculature, all of which change during childhood.<sup>6</sup> Additionally, systematic evidence of the long-term outcomes associated with medical devices that may occur months or years after the initial use or implant, would be informative for postmarket regulatory surveillance as well as for clinical decision making for physicians and families, but is not generally available.

The generation of clinical data for medical devices using conventional interventional study designs is challenging, even in adult populations, with frequent instances of small study populations, iterative and rapid design changes in devices, and ethical and practical issues with blinding and shams.<sup>7</sup> These difficulties are compounded in pediatric studies where patient populations are systematically small and events are rare, and ethical, privacy, and safety concerns can make it challenging to recruit sufficient numbers of patients to adequately power clinical studies. Finally, clinical outcomes that are used in adult studies may not be appropriate in pediatric populations. For example, replacement rates in adults may be used as a proxy for device failure, but this same measure may be inappropriate for pediatric studies because a replacement may be merely related to growth.

From the <sup>1</sup>Medical Device Innovation Consortium, Arlington, VA; <sup>2</sup>Children's Hospital of Philadelphia, Philadelphia, PA; and the <sup>3</sup>US Food and Drug Administration, Silver Spring, MD

Funding for this publication was made possible, in part, by the Food and Drug Administration (1 U01 FD 006292-01) and support from the Patient-Centered Outcomes Research Institute (PCORI) (CDRN1306-01556). Views expressed in written materials or publications do not necessarily reflect the official policies of the Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government. R.F. is an employee of the Medical Device Innovation Consortium, a 501(c)3 public-private partnership whose membership is open to industry, government agencies, nonprofit organizations, patient organizations, and professional societies. The Medical Device Innovation Consortium is funded through a combination of membership fees and federal and non-federal grants. The authors declare no conflicts of interest.

0022-3476/\$ - see front matter. © 2019 Elsevier Inc. All rights reserved.  
<https://doi.org/10.1016/j.jpeds.2019.06.060>

FDA Food and Drug Administration  
 NEST National Evaluation System for health Technology

One solution to the dearth of evidence for the use of pediatric devices is to conduct research studies using so-called real-world data, which can be defined as data that were generated in the course of routine clinical care or through activities of daily living.<sup>8</sup> Real-world data are obtained from electronic health records, health plan claims, pharmacy dispensings, and mobile technologies. A common approach for accessing these data is through the clinical information systems managed within health systems. In addition, researchers can work directly with patients through mobile application platforms, inviting them to participate in research by sharing their clinical data (eg, electronic health records) and providing patient-reported outcome data that characterize their lived experiences of illness and the effects of therapies.

Real-world data can support a variety of different types of studies. Retrospective study designs leveraging multiple types of data generated in the course of clinical care can support marketing authorization for expanded indications as well as postmarket surveillance studies to monitor safety and effectiveness. For premarket submissions, when appropriate, retrospective data can be used as historical controls in prospective studies, or for developing objective performance criteria against which the new technology can be more efficiently assessed. For example, in 2017, a pediatric ventricular assist device that provides mechanical circulatory support to bridge to cardiac transplantation for pediatric patients was approved by the FDA based in part on real-world evidence from the Extracorporeal Life Support Organization registry. The registry provided data to develop historical control data on the effectiveness endpoints for the comparator, extracorporeal membrane oxygenation.<sup>9</sup>

A significant future promise of real-world data lies in premarket randomized clinical trials that leverage electronic health records to identify, recruit, consent, and follow patients.<sup>10</sup> These trials are embedded within usual care and aim to decrease the burdens that traditional data collection processes impose on patients, clinicians, and practices; improve recruitment and timeliness; and reduce the cost of conducting clinical trials.<sup>11</sup> However, there have been no such trials to date to support regulatory submissions in the US.

To leverage the opportunities of real-world data, the FDA's Center for Devices and Radiological Health began planning in 2012 for the establishment of the National Evaluation System for health Technology (NEST), a multistakeholder-led initiative whose mission is to increase the value and use of real-world data to support medical device evidence generation.<sup>12</sup> NEST's early activities have focused on establishing a network of device manufacturers who collaborate with health providers, health payers, and coordinated networks to conduct research. PEDSnet ([pedsnet.org](http://pedsnet.org)), a network of 8 children's hospitals covering approximately 6 million pediatric patients, is the only NEST research partner devoted exclusively to pediatric research.<sup>13</sup> NEST is currently funding 20 test cases (5 of which include pediatric patients) that include evaluating the identification of historical controls for a premarket

submission, label expansions, postmarket surveillance, and active surveillance to test feasibility and establish a data and operational infrastructure that would allow such studies to be conducted at scale.<sup>14</sup>

Challenges to leveraging the full potential of real-world data remain. For example, very few health systems routinely capture a unique device identifier that specifically identifies the type and manufacturer of a device. Although the absence of a unique device identifier limits our ability to efficiently conduct retrospective device research, in many instances it is still possible to identify the use of specific devices by brand. For example, in the NEST test cases, researchers are using manufacturer registries, health system supply chain data, or internal registries to obtain these data.

Concerns about the study validity when using real-world data have also appropriately focused on the quality of the source data and the appropriateness of the analysis methods.<sup>15</sup> First, data quality issues can arise because of the lack of standardized data collection at the point of care (eg, there are dozens of ways that a record might capture even seemingly simple variables such as sex or age). One solution adopted by the institutions working with NEST is to curate and organize data generated at the point of care using standardized common data models to increase its usability for research and surveillance purposes.<sup>16</sup>

Second, to support robust clinical evidence, longitudinal patient data that include relevant clinical outcomes that occur over time are important. Pediatric patients may receive care in different systems at any point in time (especially if they are in need of complex care) and will eventually transition to adult care. Although still a challenge from a legal and governance perspective, the increasing ability to link electronic health record data with health payer claims data and the use of patient-mediated data sharing through mobile platforms improves the capacity to follow the patient over time and obtain longitudinal data for research purposes.

Third, institutions must have in place appropriate processes for checking the internal validity of data collected. Increasingly these processes are being automated, but in pediatric studies additional checks might be required to account for the multiple subpopulations between 0 and 21 years of age.<sup>17</sup> For example, age and weight variables will impact normal ranges for laboratory tests, vital signs, and drug dosages.

Finally, the use of data for purposes other than what they were originally collected for requires appropriate legal and regulatory frameworks as well as robust privacy and security policies in place at institutions to ensure patient data are appropriately protected. Following other data network models, data used in NEST are local and remain behind the firewalls of the institutions generating the data minimizing the transfer of individual-level clinical data outside of the system where care is received.<sup>16</sup>

Like the 15-mm rotatable mechanical heart valve developed for newborns and infants, many medical devices used in pediatric patients hold the potential for radically changing how we provide care to children while improving

their health outcomes. The use of real-world data captured in electronic health records and other electronic clinical information systems, such as mobile apps, can rapidly expand the evidence base for pediatric device effectiveness and safety. With the establishment of NEST, and its collaborators such as PEDSnet, evidence to support regulatory label changes, postmarket surveillance, and premarket trials will benefit clinicians and patients through more timely, comprehensive, and robust information on the safety and effectiveness of available and future medical devices. ■

Submitted for publication Apr 15, 2019; last revision received Jun 2, 2019; accepted Jun 25, 2019.

Reprint requests: Rachael L. Fleurence, PhD, National Evaluation System for health Technology, Medical Device Innovation Consortium, 1501 Wilson Blvd Suite 910, Arlington, VA 22209. E-mail: [rfleurence@mdic.org](mailto:rfleurence@mdic.org)

## References

1. US Food and Drug Administration. FDA expands approval of replacement heart valve, smallest mechanical valve size approved in the world. [www.fda.gov/news-events/press-announcements/fda-expands-approval-replacement-heart-valve-smallest-mechanical-valve-size-approved-world](http://www.fda.gov/news-events/press-announcements/fda-expands-approval-replacement-heart-valve-smallest-mechanical-valve-size-approved-world). Accessed May 31, 2019.
2. Ulrich LC, Joseph FD, Lewis DY, Koenig RL. FDA's Pediatric Device Consortia: national program fosters pediatric medical device development. *Pediatrics* 2013;131:981-5.
3. Hwang TJ, Kesselheim AS, Bourgeois FT. Postmarketing trials and pediatric device approvals. *Pediatrics* 2014;133:e1197-202.
4. American Academy of Pediatrics. Off-label use of medical devices in children. *Pediatrics* 2017;139:e20163439.
5. Samuels-Reid JH, Blake ED. Pediatric medical devices: a look at significant US legislation to address unmet needs. *Expert Rev Med Devices* 2014;11:169-74.
6. Sutherland J. Off-label use of medical devices in pediatric interventional cardiology: prerogative or necessity? *Interv Cardiol* 2011;3:549-55.
7. Faris O, Shuren J. An FDA viewpoint on unique considerations for medical-device clinical trials. *N Engl J Med* 2017;376:1350-7.
8. McMahon AW, Dal Pan G. Assessing drug safety in children — the role of real-world data. *N Engl J Med* 2018;378:2155-7.
9. US Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED) ventricular assist device. [www.accessdata.fda.gov/cdrh\\_docs/pdf16/P160035B.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf16/P160035B.pdf). Accessed May 31, 2019.
10. US Food and Drug Administration. Framework for FDA's real-world evidence program. FDA framework; 2018. [www.fda.gov/media/120060/download](http://www.fda.gov/media/120060/download). Accessed July 17, 2019.
11. Hernandez AF, Fleurence RL, Rothman RL. The ADAPTABLE trial and PCORnet: shining light on a new research paradigm. *Ann Intern Med* 2015;163:635-6.
12. Shuren J, Califf RM. Need for a national evaluation system for health technology. *JAMA* 2016;316:1153-4.
13. Forrest CB, Margolis PA, Charles Bailey L, Marsolo K, Del Beccaro MA, Finkelstein JA, et al. PEDSnet: a national pediatric learning health system. *J Am Med Informatics Assoc* 2014;21:602-6.
14. Fleurence RL, Shuren J. Advances in the use of real-world evidence for medical devices: an update from the national evaluation system for health technology. *Clin Pharmacol Ther* 2019;19:1380.
15. Krucoff MW, Sedrakyan A, Normand SLT. Bridging unmet medical device ecosystem needs with strategically coordinated registries networks. *JAMA* 2015;314:1691-2.
16. Fleurence RL, Curtis LH, Califf RM, Platt R, Selby JV, Brown JS. Launching PCORnet, a national patient-centered clinical research network. *J Am Med Informatics Assoc* 2014;21.
17. Qualls LG, Phillips TA, Hammill BG, Topping J, Louzao DM, Brown JS, et al. Evaluating foundational data quality in the national Patient-Centered Clinical Research Network (PCORnet®). *eGEMs* 2018;6:3.