



Yale Law School

Collaboration for Research Integrity & Transparency

Yale Collaboration for Research Integrity & Transparency (CRIT) Public Comment on the Food and Drug Administration’s Draft Guidance “Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices”

The Yale Collaboration for Research Integrity & Transparency (CRIT) has carefully reviewed the draft Guidance. The draft Guidance leaves open the possibility that real-world evidence could be used in multiple contexts, such as the following:

1. Expanded indications for use in approved Class III devices;
2. Compliance with post-market surveillance study requirements in Class II devices imposed under Section 522 of the Food, Drug, and Cosmetic Act;
3. Post-approval device surveillance as a condition of approval for Class III devices;
4. As a non-randomized control group for a study comparing a new device to existing devices in the same clinical indication for Class III devices;
5. As supplementary data when the FDA evaluates medical device safety; or
6. As data used to update Objective Performance Criteria (OPC) and Performance Goals (PG) used in review, comparison and evaluation of safety or effectiveness endpoints.

We are in support of appropriate use of high-quality real-world evidence in the context of post-market medical device regulation and surveillance. With the emerging availability of larger volumes of electronic data and the FDA’s emphasis on a Total Product Life Cycle approach to regulation with plans for a national evaluation system for health technology, real-world evidence has significant potential.

However, we are opposed to allowing real-world evidence as a substitute for traditional clinical trial data in the context of evaluating pre-market applications for class III devices, including applications for expanded indications for use in already approved Class III devices. Previous studies have demonstrated that when Class III devices were cleared for marketing based upon the less stringent 510(k) criteria, patients were sometimes exposed to unnecessary risks, with many resulting recalls. IOM (Institute of Medicine). 2011. *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*; Washington, DC: *Oversight of Recalls* GAO-11-468 (Washington, D.C.: June 2011); GAO, *Medical Devices: FDA's Premarket Review and Postmarket Safety Efforts*, GAO-11-556T: (Washington, D.C.: Apr 13, 2011); GAO, *Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process*, GAO-09-190 (Washington, D.C.: Jan. 15, 2009).

The use of real-world evidence in the pre-market context of Class III devices presents both safety and effectiveness concerns.

In addition, while real-world evidence can help inform our understanding of medical device safety and effectiveness in the post-market context, some aspects of the FDA's Draft Guidance could be strengthened to ensure that regulatory decisions are based on reliable, high-quality data. We suggest the following:

- The draft guidance should be revised to state that case reports would not be used in isolation to guide regulatory approval decisions (101), but only in concert with additional more rigorous studies. Additionally, we do not think that data without controls such as from non-representative patient surveys or data from patient testimonials meet this standard.
- Any real-world evidence should use an intervention and a control group.
- We are concerned about the suggestion that real-world evidence could be accepted in place of randomized controlled trials. We recommend that this section be substantially revised to clarify that such an exchange of evidence is not acceptable.

The draft guidance currently states that:

In some cases, a traditional clinical trial may be impractical or challenging to conduct, giving the realities of medical device innovation and development cycles, ethical issues that may arise with treatment assignment, and other similar challenges in executing traditional trials with high quality. (188-191).

In particular, there are multiple examples of medical devices that had been approved based on observational data because it was felt unethical to randomize patients to not receiving a device, where high-quality evidence later showed the device had no benefit. One such example is patent foramen ovale occluders for cryptogenic stroke, where clinical trials were significantly delayed, and then ultimately showed no improvement in outcomes. (see O’Gara PT, Messe SR, Tuzcu EM, Catha G, Ring JC. Percutaneous Device Closure of Patent Foramen

Ovale for Secondary Stroke Prevention: A Call for Completion of Randomized Clinical Trials: A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation *Circulation*. 2009;119:2743-2747:

<http://circ.ahajournals.org/content/119/20/2743>)) And there have been multiple examples where a randomized controlled trial using a sham control demonstrated a device to have no benefit, while prior single-arm clinical studies demonstrated substantial clinical benefit, such as renal denervation therapy for resistant hypertension (see Redberg RF *N Engl J Med* 2014;371:892-893:

<http://www.nejm.org/doi/full/10.1056/NEJMp1406388>)

- The draft guidance should be revised to state that real-world evidence should include a concurrent control group (255-257). If registries are used to fulfill pre- and post-market evidentiary requirements, then they must show that a new device performs at least as well as the current standard of care.
- The draft guidance should be clarified to limit the use of historical controls as part of real-world evidence (278). Historical controls are inferior to active controls (see Chen CE, Dhruva SS, Redberg RF *JAMA* 2012;308:1740-42: <http://jama.jamanetwork.com/article.aspx?articleid=1389607>) and can lead to greater uncertainty about device performance relative to contemporary standards

of care, particularly given today's rapid acceleration of medical technology and progress.

- The draft guidance should reject any use of real-world evidence accumulated “in a broader patient population or wider set of circumstances than described in the device labeling” (285-89). This would amount to FDA sanctioning deliberate off-label use, without adequate data to demonstrate efficacy or safety and without adequate safeguards offered through study under an Investigation Device Exemption, in the name of accumulating real-world data, potentially at the expense of conducting high-quality studies.
- The draft guidance should state that if real-world evidence is used “to conduct post-approval studies that are imposed at the time of device approval” (298-99) that such studies must be report on 1-year outcomes within 2 years of market availability. Recent evidence shows that for high-risk therapeutic devices FDA-approved via pre-market approval, only 13% of initiated post-market studies were complete between 3 and 5 years post-approval (see Rathi VK, Krumholz HM, Masoudi FA, Ross JS *JAMA* 2015;314:604-612: <http://jama.jamanetwork.com/article.aspx?articleid=2425742>).
- The draft guidance should indicate that if real-world evidence is used “to conduct post-approval studies that are imposed at the time of device approval” (298-99) that such studies enroll representative patient populations to those receiving the

device in clinical practice. Previous work has shown that participants in post-marketing studies for carotid artery stenting have different characteristics and lower mortality than nonparticipants and, thus, results for post-marketing studies may not be reliably extrapolated to the real-world population of patients receiving the device (see Yeh RW, Kennedy K, Spertus JA, et al *Circulation* 2011;123:1384-90).

- The draft guidance should request that investigators for post-approval studies register their trials prior to inception and report their results on ClinicalTrials.gov within 12 months of study completion in compliance with FDAAA Section 801 and, in addition, then publish the results in peer-reviewed journals within 2 years of study completion. Recent evidence shows that over 40% of post-approval studies for medical devices are not published 5 years after completion of the final report (see Quesada O, Yang E, Redberg RF *JAMA Intern Med* 2016;1121-3: <http://archinte.jamanetwork.com/article.aspx?articleid=2530284>).
- The draft guidance should make clear how “collection of RWD should not dictate, interfere with or alter the normal clinical care of the patient, including choice of treatment” (362-63). Specific safeguards, including informed consent and study registration, must be put in place to discourage alteration of patient care plans in order to gather real-world evidence to support, for example, expanded device indications.

- The draft guidance should state that, when feasible, specific outcomes of interest in real-world data be independently adjudicated by blinded investigators (406-8). Such independent review is necessary to reduce reporting bias.
- The draft guidance should mandate that consideration of the suitability of real-world data (418-20 and 488-9) will also include an assessment of whether the real-world data includes patient subgroups traditionally underrepresented in medical device research, including the elderly, women, and racial and ethnic minorities in similar proportions to disease prevalence and there must be analysis of study results based on those key demographic categories in line with the FDA’s Draft Guidance “Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies” and the FDA’s Final Guidance “Evaluation of Sex-Specific Data in Medical Device Clinical Studies,” particularly as this data is often missing in pre-market evaluations (see Dhruva SS, Bero LA, Redberg, RF *Circ Cardiovasc Qual Outcomes* 2011;4:165-71: <http://circoutcomes.ahajournals.org/content/4/2/165>).
- The draft guidance should indicate that informed consent must always be in place when real-world data is prospectively collected for the purposes of obtaining approval or expanding indications (498).