

Senator Patty Murray

1. **As we've discussed, FDA has jurisdiction over critical public health issues beyond the regulation of drugs and medical devices. The agency is also charged with protecting kids from the dangers posed by tobacco, giving Americans the nutrition information they need to make decisions about the foods they choose for themselves and their families, and ensuring the safety and nutritional soundness of our food supply, to name a few.**

I'm particularly eager to see full implementation of two long-awaited FDA rules – the first to ensure menu labeling in restaurants and similar establishments, and the second expanding FDA regulation of tobacco products to include e-cigarettes and other products – a rule that urgently needs to be finalized.

- a. **Can you tell me more about what your priorities will be when it comes to these kinds of public health protections?**

Finalizing the tobacco deeming rule is of the highest priority for the Agency and the Administration. We share your sense of urgency on this important matter. We are working diligently to finalize the rule as soon as possible. The rule has undergone extensive internal review within FDA and HHS and is now under review at the Office of Management and Budget.

Once the proposed rule is finalized, some provisions (e.g., establishment registration, product listing, ingredient listing, and the adulteration and misbranding provisions of the statute) in the FD&C Act would automatically apply to all deemed tobacco products. In addition, other provisions of the proposed rule would apply to covered, newly deemed tobacco products—if included in the final rule—such as: minimum age and identification restrictions to prevent sales to underage youth; requirements to include health warnings; and a prohibition of vending machine sales, unless in a facility that never admits youth.

When the rule is final, FDA will prioritize implementation, including educating industry on how to comply with the requirements in the rule. In addition, FDA considers the deeming rule to be a foundational regulation, which, once finalized, will allow the Agency to take further actions regarding critical public health issues.

With respect to menu labeling, on September 11, 2015, FDA issued the draft guidance document titled “A Labeling Guide for Restaurants and Retail Establishments Selling Away-From-Home Foods – Part II (Menu Labeling Requirements in Accordance with 21 CFR 101.11.” We currently anticipate issuing the final guidance in late spring 2016.

FDA will be focusing the first year of implementation on providing educational and technical assistance for persons and covered establishments, and for our state, local, and tribal regulatory partners to support consistent compliance nationwide. Since publication of the final rule, FDA has been very active in attending conferences as invited presenters, participating in industry sponsored webinars and conference calls, and meeting with industry representatives to help them understand the provisions of the rule and how to implement the provisions. We will continue to be available for these types of activities. In addition, we have established a special mailbox for covered establishments (CalorieLabeling@fda.hhs.gov) to contact us with their questions.

- b. Once FDA finally asserts their jurisdiction over additional tobacco products, what steps will you take to make sure the agency moves swiftly to fully use its new authority and ensure that Americans – and especially kids – are protected from the full range of tobacco products?**

FDA has vigorously enforced the youth access and marketing restrictions for currently regulated tobacco products. This includes conducting more than 522,000 retail compliance checks nationwide to ensure retailers are complying with the law, initiating enforcement action when violations are observed, and providing compliance training and education to retailers so they understand the requirements under the law. These efforts will continue for newly deemed products, once the proposed rule is finalized.

As stated above, when the rule is final, FDA will prioritize implementation of all aspects of the rule and take further actions, when warranted, to protect the public health.

- c. I know that limiting the amount of the sodium in the food supply is something the agency has been thinking about for a long time – and I’m guessing, as a cardiologist, as issue of personal interest to you. When do you think we might finally see action on this issue?**

I do have a strong interest in this issue and I can assure you that FDA is continuing to work diligently in this area, but we do not have a specified time frame for issuing a proposal.

- 2. In April 2015, Senator Isakson and I led a letter from a bipartisan group of 29 Senators to Acting Commissioner Stephen Ostroff stating “Ensuring that women have the best advice that reflects the latest nutrition science about what to eat during pregnancy, for their health and the health of their children, is of the utmost importance.” If confirmed, will you ensure that pregnant women receive final nutrition advice that is clearly presented and consistent with the latest science?**

FDA shares your interest in ensuring that pregnant women have access to sound, science-driven, and clearly understandable recommendations that enable them to make informed decisions about their diets. The final seafood consumption advice for pregnant women is undergoing interagency review. We will continue to take steps to ensure that it is reflective of the latest nutrition science. Completing the updated advice remains a priority for the Agency.

- 3. One of the many responsibilities of the Food and Drug Administration is to consider aspects of food and nutrition labeling for Americans. As you are aware, the *Dietary Guidelines for Americans* are a set of recommendations that encourage Americans to eat healthy foods like fruits, vegetables, whole grains, lean meats, eggs, and nuts. Current FDA labeling regulations, however, do not allow some of these foods to be labeled as “healthy.” Can you explain steps you would take to ensure FDA’s approach to nutrient content claims – specifically the use of the term “healthy” to make a nutrient content claim – reflect current federal dietary guidance and scientific evidence?**

The Dietary Guidelines for Americans provide information and advice for choosing a healthy eating pattern. Included in this advice are food choices that are emphasized and encouraged to help Americans move toward healthful eating patterns. Healthful eating patterns can be achieved through a wide variety of foods, not just foods that are considered “healthy” individually. The recommendations include a wide variety of food choices which may not, individually, have nutrient profiles consistent with the definition of a “healthy” claim.

FDA's regulations provide a set of minimum nutrient content standards for individual foods to be considered "healthy" and bear a "healthy" claim. A "healthy" claim can generally be used if a food contains less than 3 grams of fat, 1 gram of saturated fat, 60 mg of cholesterol and 420mg of sodium per reference amount customarily consumed.

It is possible that a food may not meet these minimum standards, yet may be able to contribute to an overall healthful eating pattern. To illustrate, a food can contribute an essential nutrient, such as calcium, to an overall healthful eating pattern, yet also contain nutrients that are recommended to be limited in the diet, such as saturated fat. This individual food could contribute to an overall healthful eating pattern, yet not be considered an overall "healthy" food by itself.

While we try to ensure that all regulations related to nutrition labeling are consistent with the Dietary Guidelines for Americans, it is important to understand that the focus of the Guidelines is healthful eating patterns. FDA will continue to monitor and assess the most recent science to update our nutrition and nutrition-related regulations as needed.

For example, we are currently working to update our requirements for the Nutrition Facts label.

4. As you know, an increasing amount of manufacturing of both active pharmaceutical ingredients and finished pharmaceutical products, as well as testing for new drug applications, is occurring in foreign countries. How can we better ensure that drugs, devices, food, and other products regulated by the FDA – that are developed and made outside our borders – meet the quality and safety standards we require in this country to protect the public?

All drugs delivered to patients in the United States are subject to the same high standards, regardless of country of origin. Registered drug manufacturing facilities in foreign countries are subject to FDA inspection, with inspection frequency determined on the basis of risk to patients. FDA employs a highly trained global inspectorate, which is skilled in evaluating processes and uncovering manufacturing problems during inspections. Whenever FDA investigators find product quality issues that potentially implicate drug safety and efficacy, the Agency takes appropriate action, which could include issuing a Warning Letter or import alert, or taking other enforcement action. Because of resources made available under the Generic Drug User Fee Amendments of 2012 (GDUFA), FDA has been able to significantly increase the number of inspections (both surveillance and pre-approval) it conducts in foreign countries (e.g., India). Having in-country investigators allows FDA to be more responsive to high-priority public health and safety issues. FDA utilizes risk-based strategies and local intelligence in order to maximize its resources to conduct timely and high quality inspections. Such strategies may include the establishment's compliance, records, and recalls-related history, as well as the inherent risks of the drug produced at the facility.

5. Please provide a description of the work that you performed in creating and leading the Duke Clinical Research Institute including what you believe is some of the most significant work you conducted or oversaw at DCRI.

The Duke Clinical Research Institute (DCRI) was established in 1996 by Duke University Medical Center (Duke) as an institutional resource for Duke faculty members conducting clinical research; including clinical trials, health services research and health policy research (www.dcri.org). I was appointed as the founding Director of the DCRI in 1996 and served in this capacity until 2006. The DCRI operates as a multidisciplinary research unit within the Duke University School of Medicine. The

mission of the DCRI is to “develop and share knowledge that improves the care of patients through innovative clinical research.”

As part of their academic endeavors, Duke faculty members pursue grants and contracts for research studies based on their individual clinical and research interests. DCRI staff provide assistance to the faculty in preparing grant applications and proposals for potential studies sponsored by government agencies, non-profit organizations, and foundations and commercial entities.

When grants or contracts are awarded, the faculty member serves as the principal investigator of a study and a team of DCRI staff members and faculty (including statisticians, project managers, data managers, regulatory associates, etc.) is assigned to perform operational and regulatory activities required for the conduct of the study. Following completion of the study, the faculty member is responsible for conducting an independent analysis and interpretation of the study results, and disseminating the results through the peer-reviewed literature and presentations at scientific meetings.

In my role as Director, my responsibilities included the following:

- Providing institutional leadership and a vision for directing the faculty towards the future of clinical research while meeting societal needs.
- Overseeing the work of faculty members and staff involved in research studies awarded to the DCRI.
- Overseeing the clinical, operational and financial performance and ensuring regulatory compliance of all research studies conducted at the DCRI.
- Ensuring the publication and dissemination of the results of studies conducted at the DCRI
- Ensuring that DCRI operational capabilities are aligned with the research interests of the faculty
- Developing a cadre of faculty members and staff who are experts in clinical research methods
- Educating and training junior faculty, fellows, and students in clinical research.
- Ensuring a balanced portfolio of research studies by funding source to achieve financial self-sustainability and being a prudent steward of institutional resources.

Significant accomplishments:

- Developed a model for academic coordination of large scale research, including direct involvement in national policies on CMS reimbursement for clinical trials, conflict of interest reporting, and management and policies for sustaining independent voice for academics and clinicians in design and interpretation of clinical research.
- Expanded from a cardiology-focused research unit to include almost 20 therapeutic areas, ranging from pediatrics to obstetrics and gynecology, anesthesiology, infectious diseases, mental health, drug abuse prevention and treatment, and others. To date, DCRI has conducted studies at 37,000 research sites in 65 countries and enrolled over 1.2 million patients.
- Served as a major hub of clinical trial networks, with federal funding from over 15 NIH Centers and Institutes.
- Established a nexus of patient registries in partnership with medical professional societies to improve healthcare quality and prevent medical errors. The registries in acute cardiac care and cardiac surgery have become national models with adoption of performance measures by CMS.

- Participated in multiple efforts on transparency of results of clinical research including major role in the development of *ClinicalTrials.gov* as a member of the Lister Hill Center (National Library of Medicine) Board and a contributor to the development of data fields and analytical efforts with the database.
- Developed one of the country's largest training programs for clinical research and expanded the program to an international reach.
- DCRI published over 800 manuscripts per year in the peer-reviewed literature.

6. Please provide a description of the work that you performed in creating and leading the Duke Translational Medicine Institute including what you believe are some of the most significant work you conducted or oversaw at DTMI.

The Duke Translational Medicine Institute (DTMI) was established in 2006 to serve as an academic home for Duke's clinical and translational research community. I was appointed as the founding Director of the DTMI in 2006 and served in this capacity until joining the FDA in February 2015. DTMI was created to expand the DCRI model to faculty across the entire translational research spectrum in concert with Duke's first Clinical and Translational Science Award from the NIH (the major translational research grant offered by the NIH at the institutional level). The mission of DTMI is to "improve individual and population health by catalyzing translation across the continuum of scientific discovery, clinical research care delivery, and global health."

The DTMI serves as an umbrella organization including the Translational Research Institute (bench to bedside research), the Clinical Research Institute (described above) and the Duke Center for Community and Population Health Improvement. It functions as integrated support structure to facilitate the efforts of faculty members to accelerate the translation of basic science discoveries into new medical therapies to advance patient care and to develop methods of improving population health through community engaged research and the use of electronic records and analytics to improve access and effective implementation of health services. DTMI provides a continuum of resources and training, such as statistical expertise, degree-granting programs, regulatory affairs, project management, and biobanking.

In my role as DTMI Director, my responsibilities mirrored those of my prior role as DCRI director, with the inclusion of a much broader scope of research ranging from pre-clinical translation to population health and community engaged research.

Significant accomplishments:

- Established the Duke Center for Community and Population Health Improvement to foster collaborations among community partners, researchers, and health system leaders with the goal of decreasing health inequities in the Southeast and across the country through studies designed to intervene at both the individual and community levels. This includes a CMS-funded project that uses geospatial mapping technology to identify residents in four counties in West Virginia, Mississippi, and North Carolina at greatest risk of poor health outcomes and implement interventions to achieve the "triple aim" of improved outcomes, better care and lower cost.
- Launched a major effort to develop innovative approaches for conducting pragmatic, patient-centered clinical trials. Served as the coordinating center for the NIH-funded Health Care Systems Research Collaboratory to increase the efficiency of clinical trials by using data from electronic health records; and the PCORI-funded National Patient-Centered Clinical Research Network to establish national networks of health systems, researchers, health care

providers, and patients conducting clinical trials that answer “real-world” questions most important to patients and their families.

- Created a regulatory affairs group to provide academic investigators with access to the regulatory expertise typically found in industry and assist them in navigating the regulatory process required to develop new diagnostic and therapeutic technologies. This group improved institutional compliance by creating a central database of regulatory submissions by Duke investigators and providing extensive training in regulatory requirements. This group is considered a model among other academic centers.
- Launched “The MURDOCK Study,” a longitudinal health study involving the populations of Kannapolis/Cabarrus County, North Carolina. The study aims to collect genetic and behavioral health profiles from 50,000 participants using participatory research methods to involve the entire community in the design and interpretation of the study. This has been described as a modern Framingham Study (a landmark study cardiovascular health). Over 11,000 participants have been enrolled to date.
- Developed a mechanism for all Duke investigators to access statistical expertise to improve research quality. The increased accessibility of these resources helped to facilitate a change in institutional culture regarding the value and importance of formal quantitative expertise, which is increasingly critical to ensure that research results are reproducible.

7. In your hearing you testified that you were unable to undertake as much as 70 percent of the clinical trial work that was proposed because industry companies were not willing to agree to DCRI’s requirements that all data from the trials be housed at DCRI. Why is it important that academic research centers maintain control of study data and why are some industry companies unwilling to agree to this requirement?

Under my leadership, the DCRI never and would never participate in coordinating a multi-site clinical trial without a contractual agreement that specifies the right to full access to the study data and to conduct its own analysis and interpretation of the data.

The independent role of the academic in the analysis and interpretation of the study data is an important element of the research enterprise. I have been a strong and consistent advocate for transparency through both www.ClinicalTrials.gov and the creation of access through independent coordinating centers. As discussed below, when industry controls the questions asked by the study, the data collection, and the analysis, there is significant bias because of the direct financial interest involved. Although academic investigators may have other biases, when they are conducting research in the context of their role as a faculty member in a university, there is a contract between the university and the industry sponsor, which includes the independent right to publish. This provides a balancing factor that I believe is important to ensure that the questions addressed by clinical trials are in the interest of patients, the data collected are not biased and the analyses have a perspective independent of the sponsor. The important role of patients and their advocates is discussed in the response to question 15.

Unfortunately, the majority of multi-site, industry-sponsored clinical trials do not have an academic coordinating center. Individual research sites that do not have coordinating center functionality do not have copies of the entire database, and if they did, they typically do not have the expertise to conduct the analyses. Thus, I believe that the role of academically based, not-for-profit coordinating centers is important to the clinical trials process.

While most major academic medical centers have some coordinating center function, there are only a limited number who are capable of conducting large multinational trials like the DCRI. The majority of

multi-site, industry-sponsored clinical trials are coordinated in-house by the sponsor or outsourced by the sponsor to a for-profit contract research organization (CRO). In the early years of the DCRI's existence, it was common for industry sponsors to be highly resistant or even unwilling to allow full access to the study data because of their view that, in the event of a negative trial result, it would not be in their financial interest for findings to be made public.

It is now customary for medical journals to require that the authors of a manuscript attest that they had full access to the data and ability to analyze the data independent of the industry sponsor. The recommendations of the International Committee of Medical Journal Editors (ICMJE) now state that "we will not review or publish articles based on studies that are conducted under conditions that allow the sponsor to have sole control of the data or to withhold publication."¹ I have been a strong and consistent advocate for transparency through both www.ClinicalTrials.gov² and the creation of access through independent coordinating centers.³ The composite of all of these efforts has changed the landscape, and industry sponsors are now much more willing to agree to independent analysis.

8. The 2011-2014 conflict of interest statements filed by you that list the names of all private companies from whom you received consulting fees or other funds are publicly available on the Duke Clinical Research Institute website. Please explain the policy of DCRI regarding submission and posting of these conflict of interest disclosures, why that policy exists, and how long it has been in place.

The DCRI, as part of Duke University, abided by University policies. Like most major universities, Duke faculty members have the right to participate in private consulting one day per work week. All consulting must be reported to the University conflict-of-interest committee, and these consulting engagements are screened for the potential of conflict of interest and conflict of commitment by relevant committee members and institutional leaders. All of this information is kept within an institutional database to ensure follow-up.

I decided to begin publicly posting my interactions with industry to set an example for transparency, and DCRI created the venue for posting. Many DCRI faculty followed suit, but it was not a requirement of DCRI policy.

9. Along with a number of other researchers at Duke University you receive consulting payments from industry companies through Faculty Connection, LLC. Please describe the purpose of Faculty Connection and the services that it performs for its consultant partners. Please include a description of the administrative fees and how excess administrative fees are used.

¹ International Committee of Medical Journal Editors. Sponsorship, Authorship, and Accountability (2007). Available at http://www.icmje.org/news-and-editorials/update_spon_sep2001.html

² [Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010](#). Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. *JAMA*. 2012 May 2;307(17):1838-47. doi: 10.1001/Jama.2012.3424. PMID:22550198.

[Compliance with results reporting at ClinicalTrials.gov](#). Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. *N Engl J Med*. 2015 Mar 12; 372(11):1031-9. doi: 10.1056/NEJMsa1409364. PMID:25760355

³ [Eur Heart J](#). 2010 Apr;31(8):911-7. doi: 10.1093/eurheartj/ehp550. Epub 2010 Feb 3.

[Towards a new order in cardiovascular medicine: re-engineering through global collaboration.](#)

Faculty Connection, LLC was established by a group of Duke faculty members to provide administrative support for the faculty when they participate in consulting activities involving private industry. It has expanded over time to include faculty from several other institutions with similar needs.

It is designed to ease and consolidate the administrative burdens on individual faculty as they participate in consultation activities with industry on personal time and create greater efficiency for their work. Among the support it provides is:

- filing administrative paperwork required by the University, including summaries to facilitate accurate reporting to university conflict-of-interest oversight committees
- ensuring compliance with legal and ethical requirements
- negotiating contracts and ensuring that the contracts are in compliance with university policy and protect the rights of academic faculty to remain independent
- billing and accounting

Payments for consulting activity are made directly to Faculty Connection, which retains 20 percent of the fees for administrative overhead (primarily to cover staff salaries), and the faculty member receives the remaining 80 percent. Since its inception, Faculty Connection has donated the proceeds not consumed by administrative costs to Duke University (and Stanford University beginning in 2013) to fund research and education activities for trainees.

In 2014, the following contributions were made by Faculty Connection to Duke University and Stanford University:

- \$15,000 to the Stanford University Department of Medicine Residency Program for house staff research
- \$30,000 to the Duke Clinical Research Institute (DCRI) fellowship fund to support current and future fellows including the adult cardiology fellows
- \$24,000 to the Duke Department of Medicine for research and pilot projects performed by residents and/or house-staff. The main purpose of the donation is to help the department encourage and support residents as they start their research careers.
- \$15,000 to the Duke Department of Pediatrics for research and pilot projects performed by residents, house-staff, and trainees to support research careers
- \$4,000 to the Duke Cancer Institute to train and provide research opportunities for the residents and or house-staff

2013 Contributions to Duke and Stanford Universities totaled \$115,000.

2012 Contributions to Duke University totaled \$154,000.

2011 Contributions to Duke University totaled \$100,000.

2010 Contributions to Duke University totaled \$ 75,000.

10. At your hearing you stated that you have a personal policy of donating all consulting fees received from industry to charitable organizations of your choosing. Is it correct that, not including funds paid toward clinical trial work conducted at Duke, all consulting fees you have received from industry have been paid to you through Faculty Connections and subsequently donated according to your long standing practice?

Yes, this is correct.

11. Please list any additional measures that you have taken to ensure that the scientific integrity of the clinical trial work you have undertaken in your career is not compromised as a result of industry sponsorship and funding.

In addition to publishing the results of all clinical trials I have conducted throughout my career, I have publicly posted my Duke conflict-of-interest information since 2006, and donated all consulting fees to charity. I have been intimately involved in the development of structural and policy changes in the global research enterprise to increase transparency and reduce bias in the conduct, analysis, and reporting of clinical trials.

For the past three decades, I have worked with global colleagues who are experts in medicine, clinical research methodology, and medical ethics to develop new mechanisms to ensure that the data obtained from individuals who consent to participate in a human experiment (i.e., a clinical trial) are evaluated by parties who do not have a financial interest in the success or failure of the treatment under study, and who, by virtue of their employment as a faculty member in a university, are guaranteed the right to academic freedom. I do not use the term “human experiment” lightly, because asking someone to volunteer for a study carries with it a responsibility to do the best job possible to ensure that the trial is conducted properly and that the result of the trial will contribute to generalizable knowledge to help future patients.

One such mechanism is the establishment of steering committees for an individual clinical trial, comprised of academic investigators from multiple institutions and countries, to serve as a collective body to interact with the industry sponsor in developing the protocol and overseeing the operational conduct of the trial. This approach minimizes the influence of any given individual, ensures inclusion of a wide range of perspectives and opinions, and provides a formal structure for decision-making. The steering committee does not include representation from the sponsor but may have one or two sponsor representatives to ensure effective communication.

Another mechanism is the use of an independent academically based analytical center which is responsible for receiving data collected during a trial, ensuring the accuracy of the data, and analyzing the data following the conclusion of the trial. These are often referred to as Data and Statistical Coordinating Centers. This structure allows the database to be maintained by a party external to the industry sponsor and for the data to be fully analyzed before the results are shared with the industry sponsor.

A third mechanism is the formation of data monitoring committees, comprised of independent experts who oversee the conduct of the trial and have access to the data to protect the safety and interests of the

research participants. I have published significant papers with colleagues to improve the function and scientific basis for data monitoring committees.⁴

Finally, the formation of a publication committee, which is now standard practice at the DCRI and other academic coordinating centers, serves as another extremely valuable mechanism for ensuring independent decision-making in the interpretation and publication of trial results. As is the case with steering committees, publication committees provide a formal organizing structure for decisions regarding both primary and secondary manuscripts, as well as a transparent and inclusive process for any investigator to propose an idea for a manuscript and to access the data in order to perform the proposed analysis. A representative of the industry sponsor is allowed to serve as a member of the committee, however, the majority of members must be academic investigators and decisions require a majority vote.

12. Earlier this year, after joining the FDA you removed your name from three journal articles published in the Journal of Clinical trials that discussed pragmatic cluster randomized trials (PCRT). You have previously advocated for using more pragmatic cluster randomized trials or pragmatic clinical trials in research. Have you previously expressed the theme and ideas contained in these articles in published articles and speeches?

The depiction of my actions with regard to these issues was inaccurate. The articles in question were part of a major joint project between the NIH Health Care Systems Research Collaboratory (“the Collaboratory”) and PCORnet, PCORI’s large national network for clinical research. I was Principal Investigator (PI) of the Collaboratory and co-PI of PCORnet. Together with Professor Jeremy Sugarman, distinguished Chair of Medical Ethics at Johns Hopkins University, we organized 10 writing teams from the two projects, in addition to some outside experts to address ethics and regulatory issues that need to be better understood as the United States moves toward a “learning health system” model. Each team was assigned to work on a specific manuscript, all 11 of which (plus one capstone summary article) were to appear together in a special issue of *Clinical Trials* (published by the Society of Clinical Trials).

At the time of my transition to FDA in February 2015, the 11 manuscripts were moving along nicely, but they were not substantially complete. For three of the 11, I had done enough work personally to be on the author list. However, upon moving to FDA, it was clear that I could no longer devote the effort needed to be acknowledged as an author. The rules governing criteria for authorship, which include substantive participation throughout the process of revision as well as final approval of the manuscript prior to submission, are clearly delineated in guidelines published by the ICMJE, to which most peer-reviewed medical journals (including *Clinical Trials*) conform. (Please see <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html#two> for details).

⁴ [Independent data monitoring committees: preparing a path for the future.](#) Hess CN, Roe MT, Gibson CM, Temple RJ, Pencina MJ, Zarin DA, Anstrom KJ, Alexander JH, Sherman RE, Fiedorek FT, Mahaffey KW, Lee KL, Chow SC, Armstrong PW, Califf RM. *Am Heart J.* 2014 Aug;168(2):135-41.e1. doi: 10.1016/j.ahj.2014.05.003.

[Data and safety monitoring boards: academic credit where credit is due?](#) Armstrong PW, Califf RM. *JAMA.* 2013 Oct 16;310(15):1563-4. doi: 10.1001/jama.2013.280383. No abstract available. PMID: 24129461

[Issues in regulatory guidelines for data monitoring committees.](#) DeMets D, Califf R, Dixon D, Ellenberg S, Fleming T, Held P, Julian D, Kaplan R, Levine R, Neaton J, Packer M, Pocock S, Rockhold F, Seto B, Siegel J, Snapinn S, Stump D, Temple R, Whitley R. *Clin Trials.* 2004;1(2):162-9. Review.

[Liability issues for data monitoring committee members.](#) DeMets DL, Fleming TR, Rockhold F, Massie B, Merchant T, Meisel A, Mishkin B, Wittes J, Stump D, Califf R. *Clin Trials.* 2004;1(6):525-31. PMID:16279293

[Monitoring and ensuring safety during clinical research.](#) Morse MA, Califf RM, Sugarman J. *JAMA.* 2001 Mar 7;285(9):1201-5. PMID:11231751

Realizing that I was unable to devote the time needed to represent responsibility for the full content of the articles, I worked with the co-authors to acknowledge my contribution in writing in each of the three articles up until the time I joined FDA—these acknowledgements are contained within the respective manuscripts. My commitment to the project and the general direction of the body of work is clearly stated in the introduction to the series, which I authored along with Dr. Sugarman.⁵

In summary, my contributions to the articles are clearly stated in the articles themselves, and I am deeply committed to the development of appropriate methods for pragmatic clinical trials and fully support the body of work represented by the articles. The details of the final recommendations are the work of the authors of the manuscripts, and as editor of the series it was not my role to agree or disagree with all detailed recommendations.

13. It has been reported that in 2014 you gave a speech to healthcare and pharmaceutical stakeholders in which you characterized some regulations as a “barrier” to innovation in medicine. Please provide additional details regarding the speech and explain what you meant by this statement.

I think you are referring to a slide I have used in multiple lectures that characterizes regulation as a barrier to disruptive innovation.

This issue is a very important one for people proposing to develop new medical therapies. Throughout my career, I have benefitted from a close relationship with the Fuqua School of Business at Duke and the many contacts it brings in the field of health economics and health management. Among the many brilliant people I have met is Clayton Christensen (“The Innovators Dilemma”), who developed the concept of “disruptive innovation.” This concept is derived from the study of the transformation of industries with the base case being the conversion of radios from the vacuum tube to the transistor. The concept is that the new product or method initially is inferior but lower priced so there is a market for it. This enables innovators to iteratively improve their product until it becomes better and supplants the old product or method. My purpose in showing this slide in multiple lectures is to explain to audiences that often include students, trainees in fellowship, and scientists who are not involved in development of medical products, why the risk and investment in biotechnology is higher than most other industries, i.e., because it is a highly regulated industry, which is in fact a necessary barrier to protect public health, as discussed below. The amount of capital needed is lower and the time to return on investment is shorter in many other industries.

I have never stated, implied, or argued that the barrier should be lowered or removed. In fact I do not believe that we should be putting inferior medical products on the market, nor do the American people want inferior products to be used in medical practice. The belief that we should have evidence of benefits and risks *before* marketing in health care has been a driving force in my career and a motivation to develop more effective, efficient and unbiased ways of conducting generalizable clinical trials and implementing quality systems for learning in health care as a focus of my academic and practical work.

In summary, the purpose of the slide is to point out an issue that is motivational for people who want to develop medical products that prevent death and reduce disability: there is a requirement to demonstrate that your product is safe and effective before you market it and that it does not put people at risk compared to the clinical care that is currently accessible. This is a good thing and forms the basis for the benefit of a strong FDA to make these determinations, and it places a special responsibility on

⁵ Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015;12(5):436-41.

innovators to develop the evidence base that can ensure the FDA (on behalf of the American public) that the product is safe and effective.

14. Are there particular FDA regulations you believe should be modified so that clinical trials can be run more efficiently and effectively?

I do not believe that new FDA regulations are needed, but there is a major need for the US system to organize around some key principles that can be enunciated through multiple venues, including FDA guidances. We are already making substantial progress in developing a more efficient and effective approach for the US built on the solid foundation of, among others: FDA's Sentinel Initiative and the existing specifications, developed in consultation with industry and other stakeholders, for submission of drug and biologic applications using common data standards and terminology; NIH's HealthCare Systems Research Collaboratory and multiple clinical trial networks; the VA's networks and million veteran cohort; DOD's commitment to research in its vast health system; and ONC's progress on interoperability.

The Precision Medicine Initiative is playing a key role as a use case to develop appropriate approaches to patient volunteers, provider participation, data standards, interoperability and ethics. My overall views on these issues are described in publications #1204,⁶ #1162⁷ and #1133⁸ on my CV. Much of this work is proceeding through the work of the NIH-FDA Leadership Council.

15. What are your ideas about how we can improve the design of clinical trials to ensure we understand the effect of new drugs and devices on subpopulations of patients, including women, children, and racial and ethnic minorities?

A rational approach to medical product development would be to include the relevant populations for whom the product is intended to be used. This would include women, children, minorities and populations identified by biological, social, or preference characteristics.

Unfortunately, it is well-documented that clinical trial populations typically are not representative of the population intended to be treated, with particular deficits in the categories mentioned above. The solutions include consideration of the following approaches, and this issue is a high priority:

- The issue of designing, conducting, and analyzing clinical trials to produce results to give patients, caregivers, providers, and policy makers adequate information about benefits and risks of therapeutic interventions in specific individual patients and populations with similar characteristics is a major challenge. Improving the situation will require a comprehensive, multifaceted approach using a concept known as "quality by design."⁹ The general tools consist of small focused trials in people with common characteristics using clinical and molecular markers and, on the other extreme, very large trials using electronic health records and quality registries to provide a low cost data system. Each circumstance is somewhat different and carefully planned trials to most efficiently answer the important questions are

⁶ Anderson ML, Califf RM, Sugarman J, participants in the NIH Health Care Systems Research Collaboratory Cluster Randomized Trial Workshop. Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. *Clin Trials*. 2015 Jun;12(3):276–286. PMID: PMC4498459

⁷ Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. *JAMA*. 2014 Jun 18;311(23):2381–2382. PMID: 24810723

⁸ Califf RM, Platt R. Embedding cardiovascular research into practice. *JAMA*. 2013 Nov 20;310(19):2037–2038. PMID: 24240926

⁹ Please see <http://www.ctti-clinicaltrials.org/what-we-do/investigational-plan/qbd-qrm> for further details about this approach.

needed. All of this needs to occur in the context of more efficient networks of research sites with standard procedures and common data standards and terminology.

- A major new advance is the direct involvement of patients, their caregivers, and advocates in every aspect of the clinical trials, including prioritization of questions, protocol design, quality oversight and analysis and dissemination. FDA is already committed to more inclusion of patients in the effort, and as it evolves, it is already clear that trials are improving as result. The rapid advance of social media is enabling inclusion of patients in a direct and interactive manner, which has the potential for enormous improvement in generalizable enrollment into studies.
- The use of biomarkers and other patient characteristics can enable small, focused trials to evaluate particular populations. When viewed in the overall context of product development this approach will be a critical tool, and the Precision Medicine Initiative will accelerate the potential.
- On the other hand, the use of integrated health systems, community clinics, and community engaged research in combination with electronic health records and registries built on informed consent and developed to improve quality offer the realistic opportunity to do much larger trials with more generalizability at a dramatically lower cost. Considerable work on this approach is already underway at FDA and it will accelerate in the upcoming year. Before joining FDA, I was the PI of the NIH-funded Healthcare Systems Research Collaboratory and Co-PI of the (PCORnet), both of which are developing the concepts and operations for this transformation of the clinical trials system (see <https://www.nihcollaboratory.org/about-us/Pages/default.aspx>).
- In conjunction with industry for drugs and biologics, there is agreement to submit data using common data standard over the next several years. This will enable FDA to look at inclusion of relevant populations much more effectively. Similar approaches are underway for devices.
- Two special populations merit consideration: pregnant women and the elderly.
 - We know little about the proper dosing of drugs in pregnant women, and the success of the treatment of congenital disorders, serious genetically determined diseases and chronic diseases of childhood has dramatically increased the number of pregnant women who must be treated during pregnancy.
 - The elderly are the most rapidly growing segment of our population but little is known about medical products in people over age 80, for example. FDA can help by calling attention to these efforts and working with industry sponsors, investigators and NIH to improve their inclusion in trials.

16. With respect to pediatric research, what else can be done to ensure that providers and parents have the information they need to help them better understand how a child will respond to a particular treatment? Do you have specific ideas about how new products can be developed to meet the unique needs of children?

The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) were passed by Congress to encourage the study of drugs and biological products in pediatric patients in order to provide adequate pediatric use information in drug and biological product labeling. FDASIA made permanent BPCA and PREA.

Prior to the passage of the laws, almost 80 percent of products contained no pediatric-specific information. Since the passage of these important laws, FDA has approved almost 600 labeling changes

to incorporate pediatric information. In addition, under PREA, sponsors submit pediatric study plans early enough in development to minimize the time from approval of a drug in adults to the addition of pediatric information.

It should be noted that some products intended for treatment of rare disorders, including rare disorders in children, can receive designation under the Orphan Drug Act, and as such, not be required to comply with requirements under PREA. However, the Orphan Drug Act is also an important and successful law that provides separate incentives for the development of products used to treat rare diseases, including rare pediatric cancers.

Additionally, under BPCA, the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) was directed to evaluate, and to the extent practicable, prioritize new and emerging therapeutic alternatives to treat pediatric cancer. Products under development for use in adult cancers are brought forward for discussion by the Pediatric Subcommittee of the ODAC after consideration by pediatric experts within FDA; advice and recommendation of outside pediatric oncology experts; and pediatric oncology advocacy groups.

If you or your HELP Committee colleagues have particular ideas in mind to further advance therapies for pediatric populations, we would be happy to discuss them.

17. There have been media reports discussing concerns with the Rocket-AF trial you led while at Duke and that ultimately resulted in FDA approval of the anti-coagulant drug Xarelto in 2011.

a. Please describe the design process for the study, and the role of the Steering Committee in determining the once-a-day dosage of Xarelto for purposes of the Rocket-AF trial.

Like other large, international Phase 3 trials in this field, the international Steering Committee and Executive Committee consisted of dozens of experts in cardiology, thrombosis, anticoagulation, and primary care. A large number of studies already had been conducted with rivaroxaban (Xarelto) when the design of the Phase 3 trial came into focus.

b. The Rocket–AF trial sought to determine if Xarelto (Rivaroxaban) once a day was non-inferior to Coumadin (Warfarin), a drug that has been on the market for many years. When the results of the trial are examined on a country by country basis is there any country where Xarelto was found to be inferior to Coumadin?

There was no significant heterogeneity of treatment effect for the comparison of rivaroxaban and warfarin across countries included in the trial. This is assessed routinely in large international trials using standard methods and closely evaluated by FDA. The results for regions of the world are displayed in the Appendix to the primary publication in the NEJM (please see reference #1039¹⁰ in the enclosed CV; the relevant data can be found in the figures on pages 21-23 of the appendix, available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1009638/suppl_file/nejmoa1009638_appendix.pdf).

c. Is data from the Rocket-AF trial publicly available?

¹⁰ Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM, ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011 Sep 8;365(10):883–891. PMID: 21830957

FDA review and sponsor submissions are available, and 27 publications are already available with another 12 in press or other stages of review/development, and several dozen more in the planning stage. The trial results are also reported in www.ClinicalTrials.gov (NCT # NCT00403767;

<https://clinicaltrials.gov/ct2/show/NCT00403767?term=NCT00403767&rank=1>). These have extensive tables of baseline characteristics, outcomes, and adverse events. Study sponsor Johnson & Johnson is working with Yale University through an open-science project called YODA (<http://yoda.yale.edu/>) that will make the raw data available upon request in the future.

d. In the four years since Xarelto has been on the market have post-market surveillance studies been conducted, and what have they shown regarding the safety and efficacy of Xarelto?

Over 190 clinical trials are now registered in www.ClinicalTrials.gov involving rivaroxaban. In addition, numerous registries and observational studies have been undertaken. Finally, FDA uses post-marketing surveillance, including its Sentinel Initiative, to monitor the safety of marketed drugs, but as noted in the article by Dr. Ellis Unger (“Atrial fibrillation, oral anticoagulant drugs, and their reversal agents <http://www.fda.gov/Drugs/NewsEvents/ucm467203.htm>), the safety of rivaroxaban has been a special area of interest. No signals have been announced by FDA, and the article offers reassurance.