

A Preview of the PRESERVE IVC Filter Study

Interventional radiologist Matthew Johnson, MD, FSIR, the Society of Interventional Radiology's former liaison for the US Food and Drug Administration and co-chair of the SIR/SVS IVC Filter Task Force, discusses the anticipated launch of a large-scale, multispecialty prospective study evaluating inferior vena cava filter use and follow-up protocols to improve patient care.



How would you describe the effect of the August 2010 US Food and Drug Administration (FDA) warning letter concerning a perceived increase in inferior vena cava (IVC) filter-related complications, both in terms of patient perception/subsequent interactions and on the overall vascular community?

The FDA stated that doctors who placed filters (and the patients who had them) should consider the removal of retrievable filters when it was clinically appropriate to do so in an appropriate public health alert. However, some doctors and patients interpreted the FDA advisory as the need to remove retrievable filters regardless of circumstances, such as placement duration and the presence or absence of complications. The FDA alert affected doctors greatly in that there was a dramatic increase in calls, often several times a day, from patients who had filters or doctors whose patients had filters and wanted them removed. They wanted to know how to treat their patients appropriately.

The alert gave the impression that retrievable filters were possibly dangerous. SIR indicated to the FDA

that the communication was misleading regarding the indication and selection of permanent versus retrievable filters; however, some real concerns were raised and needed to be evaluated. The FDA, medical societies, and industry all agree that there is a concern about safety and efficacy of IVC filters.

After the issuance of the letter, you spoke at the 2011 Society of Interventional Radiology (SIR) Annual Scientific Meeting of a desire to align doctors of various society and training backgrounds, industry, and US regulatory bodies. At VIVA 2012, you announced the upcoming start of a new prospective study aimed at doing just that. What can you tell us about the process by which you and your collaborators went about joining these parties? Where did you start?

Great question. The FDA's medical alert in August 2010 generated a firestorm, and it obviously wasn't just within my society, SIR. Other physicians placing filters, specifically vascular surgeons, were also met with the same requests and concerns. Independently, we at SIR

wrote a letter in response to the FDA stating that we agree that there are concerns, and we wanted to join them in a process to evaluate filter use. Meanwhile, doctors from the Society for Vascular Surgery (SVS) did the same thing. Very soon, FDA representatives and SIR and SVS members discussed collaborating on a conference call in October 2010. Our first meeting together was in November in New York. It was then when I first met vascular surgeon David Gillespie, MD, FACS, who is co-chair with me of the multispecialty IVC filter task force that we put together. The group also includes Drs. Rodney A. White, MD, FACS; SIR Secretary James B. Spies, MD, MPH, FSIR; and Jeanne M. Laberge, MD, FSIR, as well as Susan E. Sedory Holzer, MA, CAE, and Rebecca Maron, CAE, the respective executive directors of SIR and SVS. The group collectively discussed the ideal ways to respond to the FDA's stated concerns and what kind of study was needed.

SIR and SVS representatives subsequently met in early 2011 at FDA headquarters, where we gave presentations on what we thought would be appropriate methods to conduct a study. That was when we first decided that a prospective accrual of data from patients throughout the nation receiving all types of filters would be the best methodology. Over the course of the next year, we met several times and had multiple conference calls discussing how best to accomplish that. We worked out the framework of the study, then the specific details.

What are the specifics of the study—from the number of sites and patients included to the protocols that will structure it? What will be the inclusion, exclusion, and follow-up protocols, and how were these decided?

The specifics of the study will not be known until this is approved by FDA as an investigational device exemption (IDE) study with HIPAA compliance. The current draft protocol is intended to enroll patients and accrue demographic data, following subjects for 2 years with imaging. Upon enrollment and at 3 months, we anticipate obtaining films of their abdomens, followed by computed tomography scans at 1 year and 2 years afterward. We will keep track of why the patients had their filters placed and why the filters were or were not retrieved. Even after retrieval, we will follow patients out to 3 months after retrieval. We are targeting enrollment of about 2,500 patients at 50 centers in the US. Our target population would optimally be composed of all patients in whom filters are placed at enrolling centers. We want the study to represent the current practice of filter placement and removal in the US.

The goal is to gain a functional view of all of the filters that are being placed in the US. Filter manufacturers have been brought onboard and have agreed in principle to support this trial. It has been a long process that has involved multiple regulatory bodies of the government, multiple societies, and the companies that make the filters.

What has the FDA's role in this process been, and how will the agency be involved going forward?

FDA representatives have been helpful from the beginning in stating what questions they wanted us to answer and what the major concerns were from a review of the data regarding complications and in their very extensive review of the literature. They have also been helpful providing epidemiological support to estimate how many people would be needed in the study. The FDA has been instrumental in moving the study forward.

What will industry's role be? Will they provide funding as well as direction and oversight, or more one than the other?

Corporate representatives have been involved and have committed to being the primary funding source. This initiative could not be done without their involvement and support. We have shared information with them at each step, where the draft protocols are, and we have listened to their questions and concerns—revising protocols when appropriate. There are eight related manufacturers; at this point, five have agreed to support the study.

Will data be segmented by device or presented as part of a larger pool of all approved devices without specifying outcomes with any in particular?

Both. Part of the current study design is that there will have to be a minimum number of each available device enrolled to allow evaluation of specific devices. In order to do that, there will have to be hundreds of each enrolled device. The exact number is not yet known because we still have to go through the complete protocol, thus allowing us to identify the precise number; however, it will be in the realm of a few to several hundred. We will gain an understanding as to how each device behaves, if there is a class effect, whether all devices fulfill a function, and if all devices have certain minimal or maximum levels of a complication. SIR and SVS believe that all IVC filters should not be considered as a single device because they do behave differently.

Were interventional cardiology and vascular medicine specialty groups also sought for involvement in planning and participation in the registry?

We will be evaluating filters placed by all vascular specialists. When we determine which medical centers' hospitals will be participating, we will not exclude any doctors within those hospitals. SIR and SVS independently contacted the FDA and took the lead with this project. Clearly, we would like to get a cross-section of filter placement in the US. We want to know how vascular specialists perform it, how they think about it, and why they do or do not retrieve the filters.

How will it be determined who is participating in the study?

Formal plans for enrolling centers have not yet been made, but we agree in principle that we will choose participating centers with a goal of giving us the best cross-section of US-based filter use, with all of the available devices being represented as equally as possible.

What kinds of information will be gathered, and how will the data ultimately be pooled and reported? Will they be shown by specialty of treating physician/division as well as hospital size and type?

Initially, what we want to do is answer the FDA's questions regarding safety and effectiveness and how many filters are placed off-label in patients who don't have the FDA-cleared indication. We believe that the majority of filter placements are currently off-label. The FDA-cleared indication for filter placement is prevention of recurrent pulmonary embolus. If a person doesn't have clot and a filter is placed prophylactically, that's an off-label use of a device that may have complications, such as perforation, fracture, embolization, or migration—and we want to know more about that. We want to know whether these filters are safe as a class, as individual devices, and whether they do what they're supposed to do—prevent pulmonary embolism. That gets into why we have designed the study as we did. If the major concern were only to determine whether filter placement is useful in a prophylactic population, then we would conduct a study of the prophylactic population. We're concerned about the overall safety and efficacy of filters. There are a huge number of filters being placed in the US compared to the rest of the world, with many of them being prophylactic. We want to know if that is good for US patients.

Aside from that, I don't currently have an answer to the doctor and hospital demographic question, but hopefully an enormous amount of data will become available.

During your VIVA presentation, you mentioned that a randomized controlled trial in this setting would not be ethical. Can you please share your thoughts on PRESERVE's stated goal of shifting toward a recognition that prospective registries can be used to test safety and effectiveness.

The ethics and obstacles involved in attempting a randomized controlled trial to study filter use are prohibitive, to say the least. SIR, SVS, and the FDA believe that a prospective study along these lines represents the best methodology we currently have to answer our question. There is no control group; however, there is mandatory follow-up, and there is a denominator: Optimally, every individual who gets a filter will be entered into the study. This is very different from only entering data for patients, as one desires. The goal is to have data for everyone with filters of any type at participating centers.

FDA representatives have stated that they would consider giving a new indication for prophylactic use if the data support it in this trial. This trial is important because it includes all the groups involved in filters—the doctors, the manufacturers and representatives from regulatory bodies—working together almost from the beginning of the determination that there are questions and actually collaborating on what we would need to do to answer them.

What still needs to happen before the study begins?

Right now, SIR and SVS are forming a joint foundation to oversee the study—again showing that this is a paradigmatic, collaborative undertaking. The next steps are to make the final choice for a contract research organization (CRO), complete protocol development, and submit the study for IDE approval; this all awaits the creation of our joint oversight group to oversee the contract research organization. We are working to finalize these important elements and will announce more on the start of the PRESERVE (PREdicting the Safety and Effectiveness of Inferior Vena Cava Filters) study once they are in place. ■

Matthew Johnson, MD, FSIR, is Professor of Radiology and Surgery at Indiana University School of Medicine and director of interventional oncology at Indiana University Health in Indianapolis. He has disclosed that he is on the speaker's bureau for Bayer AG and is a paid consultant to Boston Scientific Corporation, Cook Medical, CeloNova BioSciences Inc., and Nordion. Dr. Johnson may be reached at mjohnson@sirweb.org.