FDA INSIGHTS

Achieving Follow-Up Compliance

Imaging follow-up is integral to assessing device function and aneurysm stability, but patient compliance is challenging.

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Follow-up compliance is not only important when evaluating endovascular graft performance in clinical studies but is also imperative for good patient care. Adequate imaging studies are needed to assess device function and aneurysm stability. For example, prevention of aneurysm rupture can only be achieved with necessary interventions if problems, such as significant endoleaks or migration, are identified in a timely fashion. Unfortunately, imaging compliance is not often optimal during clinical studies, with diminished compliance over time, and it is even worse outside of studies.[1,2]

One of the responsibilities of a sponsor of an investigational device exemption (IDE) application is to provide progress reports to the Food and Drug Administration.[3] A critical element of these reports is the list of deviations from the investigational plan, such as failure to collect data in accordance with the clinical protocol for the IDE. Review of these reports for endovascular grafts has identified challenges with consistently obtaining adequate follow-up. As a result, sponsors have frequently been asked to describe measures they have taken to improve follow-up compliance.

To get a broader understanding of the positive and negative influences in obtaining follow-up, as well as successful and unsuccessful methods to improve follow-up, a survey was sent to six manufacturers and nine clinical investigators. Four manufacturers and four clinicians returned completed surveys. The four investigators have participated in both manufacturer- and sponsor-investigator studies.

Survey respondents indicated that they had the lowest compliance for patients treated with marketed devices and for patients enrolled into surgical control arms of studies. Generally, they indicated that they had high compliance for patients who received endovascular grafts treated under clinical studies but had significant comment regarding the challenges in getting good compliance.

CHALLENGES IN OBTAINING FOLLOW-UP

Those surveyed were asked to rank, from 1 to 5, the top challenges in obtaining follow-up. Examples of patient, following physician, and administrative factors were provided in the survey, as well as room for specifying other challenges. The results are presented in Table 1.

Each challenge was assigned a numeric value based on the number of each assigned rank from the compiled surveys, with a ranking of 1 equivalent to 5 points, a ranking of 2 worth 4 points, a ranking of 3 worth 3 points, a ranking of 4 worth 2 points, and a ranking of 5 worth 1 point.

Based on the compiled surveys, patients' unwillingness to return for follow-up obtained the highest score (35 of a possible 40), with inadequate data collected by the following physician obtaining the second highest score (25). Poor coordination of follow-up and the lack of submission of follow-up data by following physicians had the third and fourth highest scores (21 and 20, respectively). Inadequate staffing had a score of 16, and reimbursement issues had a score of only 4. A lack of interest by the investigational site and Institutional Review Board (IRB) or Heath Insurance Portability and Accountability Act (HIPAA) were written in as significant issues. Of note is that the ranking of the listed challenges was similar for manufacturers and clinicians.

MEASURES TO OBTAIN FOLLOW-UP

Those surveyed were asked to rank, from 1 to 5, the most successful measures they have taken to obtain follow-up and to indicate measures they have attempted but were unsuccessful. Examples of several strategies were provided in the survey, as well as room for specifying other methods. The results are presented in Table 2.

The measures to obtain follow-up were scored in a manner consistent with the challenges in obtaining follow-up, described previously. Personal communication

TABLE 1. MAJOR CHALLENGES IN OBTAINING FOLLOW-UP

Challenge	Score	1		2		3		4		5	
		M	I	M	I	M	I	M	I	M	I
		Total		Total		Total		Total		Total	
Patients unable or unwilling to complete follow-up	35	2	3	1	0	1	1	0	0	0	0
		5		1		2		0		0	
Inadequate data collected by following physician	25	0	1	3	1	0	0	1	0	0	2
		1		4		0		1		2	
Poor coordination of follow-up at center	21	1	1	0	1	1	0	1	1	0	0
		2		1		1		2		0	
Information not provided by following physician	20	0	2	0	1	0	1	1	0	1	0
		2		1		1		1		1	
Inadequate staffing	16	0	0	0	0	1	2	1	2	1	0
		0		0		3		3		1	
Reimbursement	4	0	0	0	0	0	0	0	0	2	2
		0		0		0		0		4	
Lack of interest by sites*	5	1	0	0	0	0	0	0	0	0	0
		1		0		0		0		0	
IRB or HIPPA issues*	3	0	0	0	0	1	0	0	0	0	0
		0		0		1		0		0	
Core lab delays	0	0	0	0	0	0	0	0	0	0	0
		0		0		0		0		0	

M, manufacturer; I, investigator.
**Written in as other reasons.*

with following physicians received the highest score (24 of a possible 40). Notification of requirements for follow-up via mail to following physicians, training of investigators and coordinators, electronic management of follow-up due dates, and adequate staffing each received a similar score (13, 13, 12, and 12, respectively). Additional measures were identified as less successful, including providing reminders to sites of when patients are due for follow-up (7), obtaining adequate informed consent (5), requiring follow-up to be completed at the center where the device was implanted (3), and providing imaging instructions (2).

Several measures were identified as having been tried and found not to be successful. The respondents identified these measures with an "X" in the survey sheets. The most common measure identified as being unsuccessful was the signing of investigator agreements by following physicians, as noted by five respondents. Four respondents also identified monetary incentives as being tried but unsuccessful. Standardized administrative procedures, imaging instructions, patient reminders to sites, and adequate staffing were each identified by two respondents as unsuccessful. One respondent found having follow-up completed at the investigational site to be unsuccessful, and one respondent indicated that obtaining informed consent was not successful.

Based on the information provided, it seems the manufacturers have attempted more methods to improve follow-up as compared to the responding clinicians. Adequate staffing was only identified as an important requirement for obtaining follow-up by the responding clinicians and not the manufacturers.

NARRATIVE RESPONSES

The survey asked for a narrative of the respondents' experiences with patient follow-up compliance. Based on the comments provided, the perception is that getting patients to understand the need for follow-up and convincing them to return to the investigational site where they were treated are the most significant challenges. Contributing factors include:

- the limited mobility of many patients;
- patients are unwilling to incur the cost of transportation to return to the implanting site;
- patients are unlikely to return for follow-up if they are feeling well;
- patients believe that there must be something wrong if they need to come back;
- patients are often elderly, have multiple medical

TABLE 2. MEASURES TO OBTAIN FOLLOW-UP

Measures	Score	Total	1		2		3		4		5		X*	
		X	M	I	M	I	M	I	M	I	M	I	M	I
			Total		Total		Total		Total		Total		Total	
Personal communication with following physicians	24	0	2	2	0	0	1	0	0	0	1	0	0	0
			4		0		1		0		1		0	
Notification of requirements for follow-up via mail to following physicians	13	0	0	0	3	1	1	0	0	1	0	0	0	0
			0		4		1		1		0		0	
Training of investigators and coordinators	13	0	0	0	0	1	0	1	3	0	0	0	0	0
			0		1		1		3		0		0	
Electronic management of follow-up due dates	12	0	1	0	0	0	0	0	1	1	1	2	0	0
			1		0		0		2		3		0	
Adequate staffing	12	2	0	1	0	1	0	1	0	0	0	0	2	0
			1		1		1		0		0		2	
Patient reminders to sites from sponsors	7	2	0	0	1	0	1	0	0	0	0	0	1	1
			0		1		1		0		0		2	
Adequate informed consent	5	1	0	0	0	0	1	0	0	0	1	1	0	1
			0		0		1		0		2		1	
Require follow-up to be completed at center where device was implanted	3	1	0	1	0	0	0	1	0	0	0	0	0	1
			1		0		1		0		0		1	
Imaging instructions	2	2	0	0	0	0	0	0	0	1	0	0	2	0
			0		0		0		1		0		2	
Statements of purpose	0	2	0	0	0	0	0	0	0	0	0	0	1	1
			0		0		0		0		0		2	
Monetary incentives	0	4	0	0	0	0	0	0	0	0	0	0	2	2
			0		0		0		0		0		4	
Signing of investigator agreement by following physician	0	5	0	0	0	0	0	0	0	0	0	0	3	2
			0		0		0		0		0		5	
Frequent monitoring	5		1	0	0	0	0	0	0	0	0	0	0	0
			1		0		0		0		0		0	
Positive reinforcement	1		0	0	0	0	0	0	0	0	1	0	0	0
			0		0		0		0		1		0	

M, manufacturer; I, investigator.
**Measure attempted but not successful.*

problems, and are cared for by multiple physicians and specialists;
- other medical issues may take priority, especially if there are no symptoms related to the aneurysm treatment; and
- patients may need to have appointments at separate facilities for clinical and imaging follow-up.

To address patient-related factors, respondents stressed the need for optimal communication and the development of a good rapport with patients. Suggested approaches included stressing the importance of follow-up during the informed consent process with an emphasis on the following:
- reminding the patients that they have a foreign object in them, which will need monitoring;
- explaining that the treatment does not remove the aneurysm, so the aneurysm must continue to be monitored;
- clarifying that there is a lack of long-term data on these devices, again emphasizing the need for monitoring;
- if the patient is to be entered in a study, explaining why it is important to have the follow-up that is required by the protocol; and
- identifying potential challenges with returning for appointments (eg, length of travel between home and the investigational site) and proactively address these issues and suggest solutions.

Continued communication with patients after the consent process was stressed, including personal contact, rather than written, if possible. The respondents suggested scheduling patients for follow-up early in the interval window to allow time for rescheduling if necessary. Patients should be called within 1 or 2 weeks of a scheduled appointment as a reminder and after the scheduled appointment, if missed. Preferably, patients should continue to be contacted even if they have missed several visits (ie, if they have not withdrawn from the study) because longer-term data will likely reflect earlier device performance.

When patients are not able or willing to return to the implanting site for follow-up, local facilities are left with the responsibility to appropriately monitor patients. These facilities must be willing and able to follow applicable protocols or labeled recommendations regarding patient follow-up. To optimize the potential to obtain adequate follow-up, communication with the following physicians becomes as important as communication with the patient.

In addition to communication, other suggested measures to improve compliance were identified. Providing reimbursement for travel expenses to patients was suggested as a possible measure to encourage patients to return for follow-up. Respondents suggested that sponsors should emphasize the importance of long-term compliance to the protocol at investigator meetings and at study coordinator meetings. The need for close monitoring of follow-up compliance at each investigational site was emphasized, with early intervention when problems are identified. Qualified study coordinators were acknowledged as critical to ensure proper follow-up, as well as the need for retraining when there are staff, principal investigator, or protocol changes. Although there was agreement that investigator commitment to the study is critical to ensure the proper conduct of the study, little insight was provided regarding how this could be accomplished. Publishing rights and regulatory requirements were not found to offer much of an incentive to clinicians. The only motivating factor identified was the ability to access novel technology.

In the US, participation in clinical studies is necessary to have access to novel endovascular graft technology. This requires complying with all aspects of the specified investigational plan. As such, potential investigators must review and agree to the plan, including the timing and type of imaging required. In addition, they must have the resources and commitment to follow imaging protocols, ensuring that imaging is not only completed, but also adequate to assess critical endovascular graft parameters. Outside of clinical studies, clinicians should reference the approved device labeling for recommendations regarding patient follow-up.

CONCLUSION

Until endovascular grafts can be designed to eliminate the potential for failures and data are available to verify adequate long-term performance, patients will require close surveillance, despite the challenges noted previously. Failure to obtain adequate follow-up jeopardizes patient safety and may negatively affect device availability.

Collaboration between investigators, following physicians, sponsors, and the FDA are important in optimizing follow-up plans, device labeling, and patient education, and their communication is necessary to improve patient follow-up compliance. ■

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