Conducting a Physician-Sponsored Investigational Device Exemption:

LAYING THE REGULATORY GROUNDWORK FOR SUCCESS

Introduction

According to 21 CFR 812, a Sponsor-Investigator is "an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used". When a Sponsor-Investigator conducts a device study it may be referred to as a Physician-Sponsored IDE (PS-IDE). A PS-IDE study may consist of a single research site where all study activities are performed, or can be multi-centered if the Sponsor-Investigator chooses to conduct the trial at additional sites. However the PS-IDE is organized, the overlying principle is that the individual conducting the study must conduct and oversee the study according to the Food and Drug Administration (FDA) regulations governing both investigators and sponsors.

Chaos can sometimes ensue when one begins down the path of a PS-IDE. This white paper will attempt to make sense of that chaos by providing a brief overview of initiating a PS-IDE, the responsibilities of the investigator, the additional sponsor responsibilities assumed by the Sponsor-Investigator, and a thoughtful discussion on the records and reports of the Sponsor-Investigator. A table detailing relevant FDA warning letter findings issued to Sponsor-Investigators and some suggestions to ensure a well-controlled clinical study will be included.

Initiation of a PS-IDE

It All Starts With an Idea

There are various motivations for conducting a PS-IDE. Perhaps a brand new medical device is created, maybe one that already exists is going to be used in a novel way, or maybe a new procedure was developed to use an existing medical device. Whatever the scenario, this cutting edge scientific advancement needs to be proven safe and effective for use with humans prior to marketing it to the public in the United States. Once the idea is born, that individual can begin the process of conducting a PS-IDE to achieve this goal.

The IDE Application

A PS-IDE starts with a Sponsor-Investigator compiling all of the necessary parts of an Investigational Device Exemption application and submitting them to the FDA. 21 CFR 812 Subpart B contains the regulatory requirements, or instructions, on how to submit the application. A PS-IDE cannot begin until the FDA provides the Sponsor-Investigator with regulatory approval to conduct the IDE. The application and accompanying materials must be submitted in triplicate by mail or in person to the Center for Devices and Radiologic al Health (CDRH) at the address listed in 21 CFR 812.19. The details of what the application must include are included in Table 1.

Table 1

- Name and address of the sponsor (which is the same as the investigator in the case of a PS-IDE)
- Complete report of prior investigations and the current investigational plan
- Description of the device manufacturing process
- The investigator agreement and a list of all investigators who will participate
- A certification that all investigators who participate will sign the agreement
- The name, address, and chairperson of the IRB responsible for reviewing the study locally
- The name and address of any institution at which part of the investigation may be conducted
- The amount to be charged for the device (if it is going to be sold)
- A claim for categorical exclusion under 21 CFR 25.30 or 25.34 or an environmental assessment under 21 CFR 25.40
- Copies of device labels
- Copies of informed consent forms and anything else provided to subjects to obtain informed consent
- Additional information per FDA request

FDA will then approve or disapprove the application by notifying the Sponsor-Investigator in writing of their decision. 21 CFR 812.30(a)(1) specifies that the investigation may begin if the Sponsor-Investigator has not heard back from FDA within 30 days, but the standard practice is to await the FDA's written response.

Once FDA regulatory approval is granted, the next step is to obtain IRB approval to conduct the investigation. The PS-IDE may not begin until both FDA and IRB approval are granted (21 CFR 812.110 (a)). While this may be the typical sequence of events, there is nothing that prohibits a Sponsor-Investigator from simultaneously submitting their IDE application to FDA and their initial submission to their IRB.

Investigator Responsibilities

The regulations regarding the general responsibilities of investigators are located in 21 CFR 812.100, and are summarized in Table 2 below. Having a firm knowledge of the investigator responsibilities will help a Sponsor-Investigator run a more well-controlled study.

Table 2

- Wait to conduct an investigation until FDA and IRB approval have been obtained
- Conduct the investigation in compliance with the federal regulations, agreement, investigational plan, and conditions of the IRB
- Supervise the appropriate use and disposal of the investigational device(s)
- Provide accurate and current financial disclosure

Sponsor-Investigator Responsibilities

Sponsor-Investigators are responsible for not only conducting the study but also for ensuring study compliance. Suddenly, there is no one looking over their shoulder raising pertinent questions regarding the conduct of the investigation. The investigator preparing to conduct a PS-IDE will want to ensure they have a good working knowledge of the regulations governing the sponsor as well the investigator. The regulations regarding the general responsibilities of sponsors are located in 21 CFR 812.40, and are summarized in Table 3 on the next page.

Table 3

- **Wait to conduct an investigation until FDA and IRB approval have been obtained**
- **Select investigators qualified by training and experience, and provide them with materials needed to conduct the investigation properly (i.e. the investigational plan and any reports of prior investigations)**
- **Ensure proper monitoring of the investigation**
- **Ensure FDA and any reviewing IRB are informed of significant new information**
- **Ensure control of the investigation device(s) and supervise all testing of it that involves human subjects**
- **Obtain agreements from investigators**
- **Ensure the investigation is conducted in compliance with the federal regulations, agreement, investigational plan, and conditions of the IRB**
- **Obtain financial disclosures from investigators**
- **Immediately conduct an investigation of any unanticipated adverse device effect (UADE)**
- **Terminate the investigation within 5 working days if a UADE that presents an unreasonable risk to subjects is discovered**

As one can see by carefully comparing Table 2 and Table 3 above, there is overlap between the responsibilities of the investigator and sponsor. However, there are some nuances that can make the task challenging. The Sponsor-Investigator will want to have trusted, experienced resources to consult with and to monitor processes and data throughout the course of the study. The FDA is a valued resource providing a designated contact to the Sponsor-Investigator following the IDE submission. The more resources a Sponsor-Investigator can utilize the better, as even the most diligent individuals by nature will struggle at times with identifying their own mistakes.

Records and Reports

Regulations concerning records (21 CFR 812.140) and reports (21 CFR 812.150) for the sponsor-investigator are also inclusive of those for both the investigator and the sponsor. Records for the investigator are typically maintained in a regulatory binder at the site, while the trial master file (TMF) contains the sponsor's records. Approval letters from the FDA and IRB for the study being conducted, documentation to show the investigators chosen were qualified by training and experience, shipping records for the investigational product, investigator agreements, monitoring reports, and correspondence are among the documents that will be found on file in the sponsor's TMF. What happens when these documents (such as CVs and medical licenses or IRB correspondence) overlap with those on file in the regulatory binder for the investigator? Should two separate, sometimes duplicate, sets of records be maintained by the Sponsor-Investigator? One for the documents of the investigator and another for documents of the sponsor? The answer is no. As long as all of the records, as required by 812.140 are accurate, current, and complete, it is not necessary for duplicate sets of records to be maintained. Table 4 and Table 5 below summarize the accurate, current, and complete records (21 CFR 812.140) and reports (21 CFR 812.150) with timeframes required to be maintained for both the investigator and sponsor.

Table 4

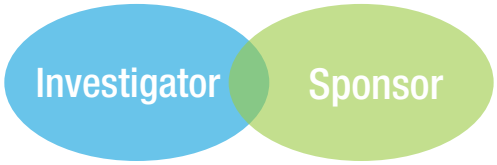
Records Required of Investigator	Records Required of Sponsor
All correspondence (including IRB submissions/approvals)	All correspondence (including IRB submissions/approvals)
Receipt, use, and disposition of device(s)	Shipment and disposition of device(s)
Adverse device effects	Adverse device effects (both anticipated and unanticipated)
Any other records FDA requires	Any other records FDA requires
Each subject's case history	Name and intended use of device(s)
Subject's exposure to investigational device(s)	Name and address of investigator(s)
Investigational plan and deviations from it	Name and address of reviewing IRB(s)
Documentation of informed consent	Statement of compliance with good manufacturing practice
	Signed investigator agreement(s)

*All records listed must be maintained for a minimum of 2 years after the latter of investigation termination or the data no longer being required for purposes of supporting a marketing application. This responsibility may be transferred if FDA is notified in writing within 10 working days. All records, including those which are identifiable must be available for inspection and copying by FDA. (21 CFR 812.140 (d))

Table 5

Reports Required of Investigator	Reports Required of Sponsor
Unanticipated adverse device effects (10 working days)	Unanticipated adverse device effects (10 working days)
Withdrawal of IRB approval (5 working days)	Withdrawal of IRB approval (5 working days)
Progress reports (at least annually)	Progress report (at least annually)
Device use without informed consent (5 working days)	Device use without informed consent (5 working days)
Final report (3 months of termination)	Final report (30 working days)
Any other report requested by FDA or the IRB	Any other report requested by FDA or the IRB
Deviations from the investigational plan (5 working days)	Withdrawal of FDA approval (5 working days)
	Current Investigator list (6-month intervals)
	Significant risk device determination (5 working days)
	Recall and device disposition (30 working days)

The Sponsor-Investigator is responsible for all of the reporting regulations of both parties, which once again contain a significant amount of overlap. The difference pertains to the line of communication that is mandated. The investigator reports to the sponsor and if required the IRB, the Sponsor-Investigator must then take it a step further and notify the FDA, if applicable.



There are also some reports that carry the same moniker. Although both the investigator and sponsor must submit a progress report, these reports are not the same document. The progress report that the investigator submits is oftentimes the IRB continuing review. Information for this report includes only what is specific to the site that the IRB oversees. Many times sponsors will collect a site's IRB continuing review report as the annual progress report requirements for the investigator. Conversely, the progress report required for the sponsor is the annual progress report that is issued to the FDA. Additionally, this annual progress report is submitted to the IRB(s) overseeing the study. The information on the annual progress report includes information from all investigative sites involved in the study, in the event there is more than one. To make this clear, even when a PS-IDE is conducted at a single site, that Sponsor-Investigator should be submitting both the continuing review progress report, as well as the study-wide annual progress report that went to the FDA, to their IRB.

Other reports exclusive to the sponsor are 5-day and 30-day supplements. These reports are used to communicate to the FDA any changes in the investigational plan. A change in the protocol that does not affect the validity of the data, the scientific soundness of the investigational plan, or the rights, safety, or welfare of the human subjects involved in the investigation may be made with a 5-day notice to the FDA. As such, the notice is to be submitted to the FDA within five days of the change. An example of a 5-day notice includes developmental changes, such as manufacturing changes, that do not constitute a significant change in design or basic principles of operation and that are made in response to information gathered during the course of an investigation (812.35(a)(3)(i)).

Changes to the investigational plan that require FDA approval are also called 30-day supplements as the sponsor-investigator must wait 30 days from submission to the FDA to incorporate a change to the investigational plan. This change does not meet the 5-day notice criteria. An example of a 30-day supplement is an increase in enrollment. To put this in a manner that many investigators will understand, these supplements may be viewed as similar to an IRB amendment submitted by an investigator at the site level which could be either expedited or full board reviewed.

It is prudent for the Sponsor-Investigator to err on the side of caution and await FDA acknowledgement of the 5-day notice. It is possible the FDA will respond that the 5-day supplement did not meet the requirements and should be pursued with a 30-day supplement. Though not required, the FDA will respond to supplements (both 5-day and 30-day supplements) and will include a supplement number with their response.

Another sponsor report that the Sponsor-Investigator should be aware of is for recalls and device disposition. The Sponsor-Investigator is to notify the FDA and all reviewing IRBs of any return, repair or otherwise disposal of an investigational device. This report or notice is to be submitted within 30 working days of the return, repair, or disposal of the investigational device. An example of this is a Sponsor-Investigator finds the investigational device broken prior to its use. The Sponsor-Investigator must notify the FDA and IRB, within 30 working days, of the disposition of the broken device (i.e., return to manufacturer or disposal).

Finally, the Sponsor-Investigator is responsible for submitting a current list of all investigators on the study to the FDA every six months. Although it is best practice for the Sponsor-Investigator to submit all reports to the FDA and then the IRB, this semi-annual report does not need to be submitted to the IRB. ICH E6 Good Clinical Practice section 8.1 contains a table of all the essential documents recommended to be maintained by both the investigator and sponsor when conducting an investigation. ISO 14155:2011(E) Annex E also contains a table of recommended essential documents.

Warning Letter Findings

A regular review of FDA warning letters can serve as a great training tool and can help Sponsor-Investigators take note of common findings from site inspections. For this whitepaper, we searched the term "Sponsor-Investigator" on FDA's website. The search returned 22 matches dating back to 2001. This list was reduced to 14 warning letters by selecting only those that were issued to actual Sponsor-Investigators. The list was further reduced to nine by removing five warning letters issued to Sponsor-Investigators of investigational new drug (IND) applications. The remaining nine warning letters were reviewed with a focus on common findings pertaining to records and reports, given the focus of this whitepaper. Tables 6A through 6J contain a breakdown of commonly cited findings by investigator and sponsor across the warning letters pertaining to records and reports that were reviewed.

Table 6A

Failure to obtain investigator agreements (21 CFR 812.43 (c))

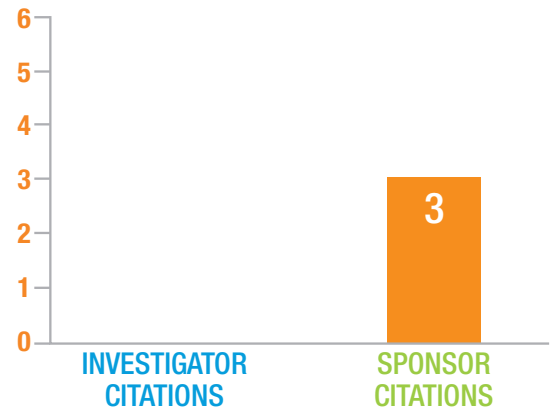


Table 6B

Failure to submit an IDE supplemental application to FDA for approval prior to changes to an investigational plan (21 CFR 812.35)

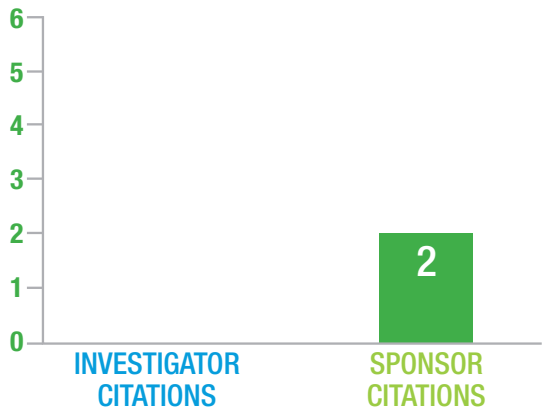


Table 6C

Failure to conduct the investigation in accordance with the investigational plan (21 CFR812.43 (c)(4)(i) and 21 CFR 812.110 (b))

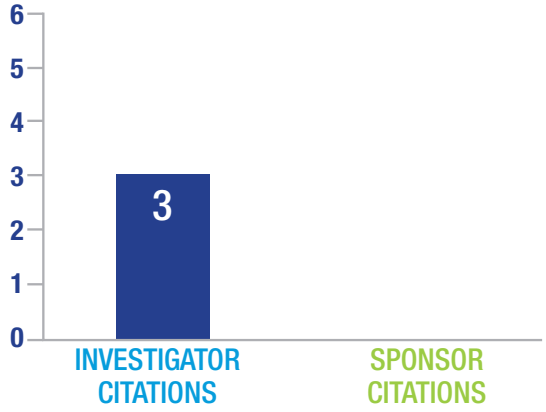


Table 6D

Failure to obtain informed consent in accordance with 21CFR 50 (21 CFR 812.100)

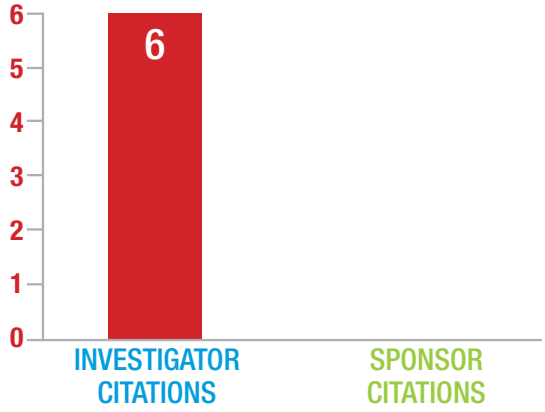


Table 6E

Failure to ensure proper monitoring (21 CFR 812.43(d))

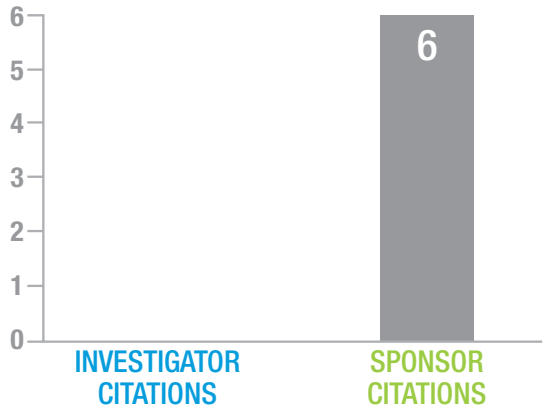


Table 6F

Failure to obtain FDA/IRB approval prior to conducting an investigation (21 CFR 812.42 and 21 CFR 812.110(a))

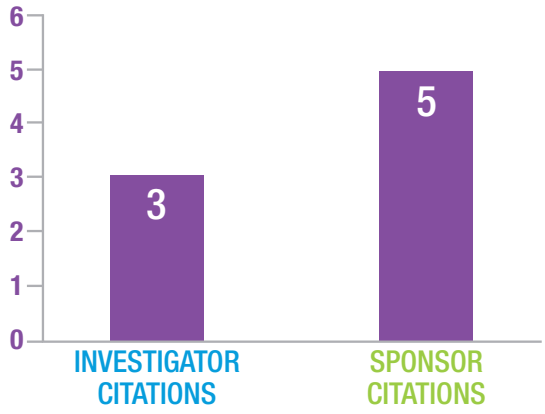


Table 6G

Failure to submit reports of withdrawal of IRB approval (21CFR 812.150 (b)(2))

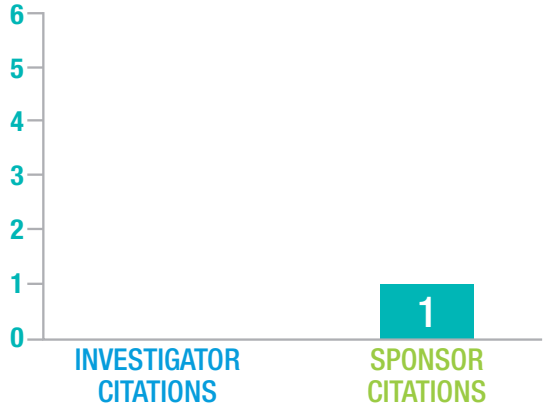


Table 6H

Failure to prepare and submit progress reports at regular intervals (21 CFR 812.150 (b)(5))

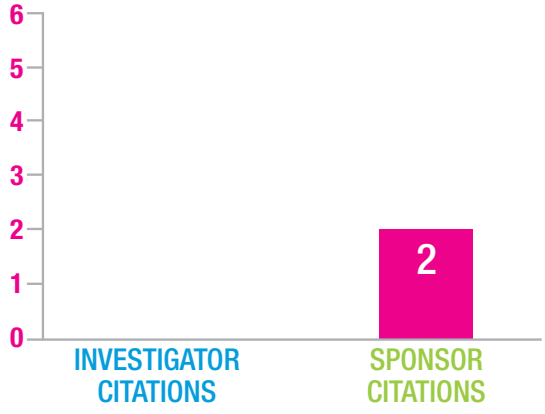


Table 6I

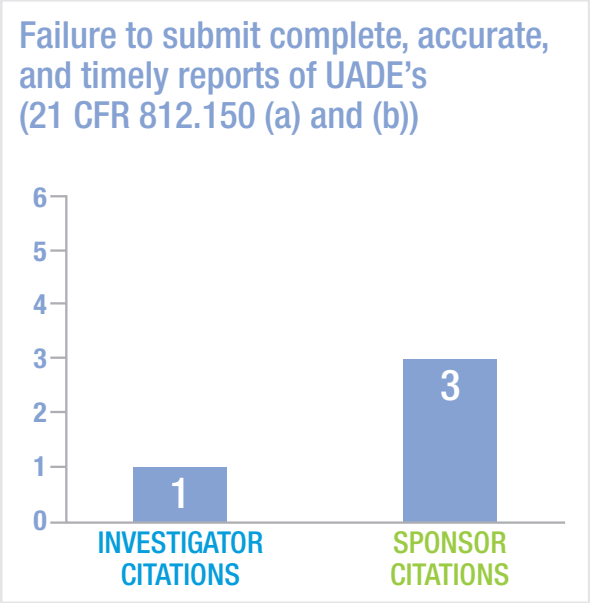
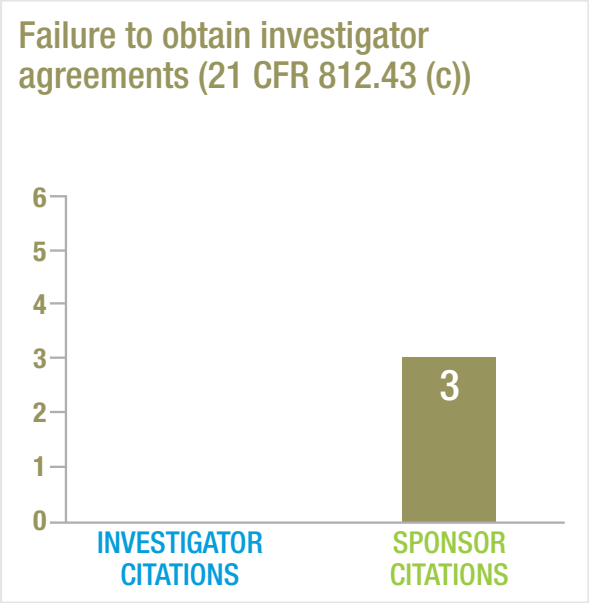


Table 6J



The importance of setting the study up for success from its onset can not be emphasized enough. Implementing the Franklin Covey philosophy to "begin with the end in mind" will help ensure a well-controlled study in which patients are protected and data has integrity.

Some recommendations for a successful start include:

- Hire a monitor who is not only qualified by training and experience to monitor a PS-IDE but who is in no other way affiliated with the study (i.e., don't have the study coordinator also be the monitor)
- Develop standard procedures specific to the site and specific to the sponsor
- Construct a communication plan, including the intended plan for documenting the communication. Commit to documenting what you already know (i.e., if you as the investigator created the amendment to the protocol along with your co-investigators, still document that training occurred as it becomes easy to take things for granted when you're wearing two hats). Include yourself as a recipient on correspondence, such as electronic mail for communication such as the annual progress report
- List all the possible documents and where they will be kept
- Consider hiring an outside auditor to inspect the study documents and processes.
- Conduct warning letter reviews yourself at monthly study team meetings to assess how you stack up.

Conclusion

In closing, conducting a PS-IDE can be a challenging task which requires a Sponsor-Investigator to wear two hats. Having monitored PS-IDE studies we have witnessed firsthand not only innovative but successful ways these dedicated physicians accomplish this feat. It is our sincere hope that this whitepaper can serve as a resource for those wishing to conduct a PS-IDE study.

Jeannine Ramsey, Lead Clinical Research Associate/Clinical Auditor

Jeannine's contributions to IMARC's standard operating procedures, training, and clinical monitoring efforts epitomize efficiency. As a site liaison, she also assists sponsors, investigators and CROs during the device and drug research process. Her expertise extends to conducting site initiations and periodic site visits; reviewing informed consents for FDA and HIPAA compliance; and training research coordinators and physicians on study protocols and federal regulations/requirements for clinical studies.

In addition to strong clinical research skills, Jeannine's extensive nursing experience includes positions as a Utilization Review Nurse and Obstetric Nurse at EMH Regional Healthcare System, School Nurse at Lake Ridge Academy, Pediatric Home Healthcare Nurse at University Hospital Health System Home Care and Neonatal Intensive Care Unit Nurse at University Hospital Health System. At EMH, she also held a Quality Clinical Analyst post. Additionally, she has experience providing chemotherapy to both pediatrics and adult patient populations.

Shawn Kennedy, Clinical Research Associate

Shawn's introduction to working in clinical research was as a Clinical Research Coordinator at Case Western Reserve University. For seven years, he coordinated trials for the adolescent psychiatry department for over ten different studies – both industry- and NIH- sponsored. Shawn joined IMARC as a clinical research associate in March of 2012.

While at IMARC, Shawn has worked in various therapeutic areas, with much of his experience including various treatments for aortic aneurysms. He is also a part of IMARC's physician-sponsored IDE team, monitoring for studies where the physician holds the responsibilities of both the sponsor and the site. Shawn's background as a research coordinator has been extremely helpful as he truly understands what it takes to do the job. He immediately forms strong relationships with sites and consistently receives praise from sites and sponsors alike for his helpful approach and attitude. Shawn is also a strong resource in the office for newer CRAs and has assisted in the orientation program for new monitors.

For more information on how you can help prepare your sites for a better outcome, starting from Day One, please contact John Lehmann at 440.801.1540 or via e-mail at jlehmann@imarcresearch.com.

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22560 Lunn Road, Strongsville, Ohio 44149 • tel 440.801.1540 • fax 440.801.1542
info@imarcresearch.com • imarcresearch.com

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