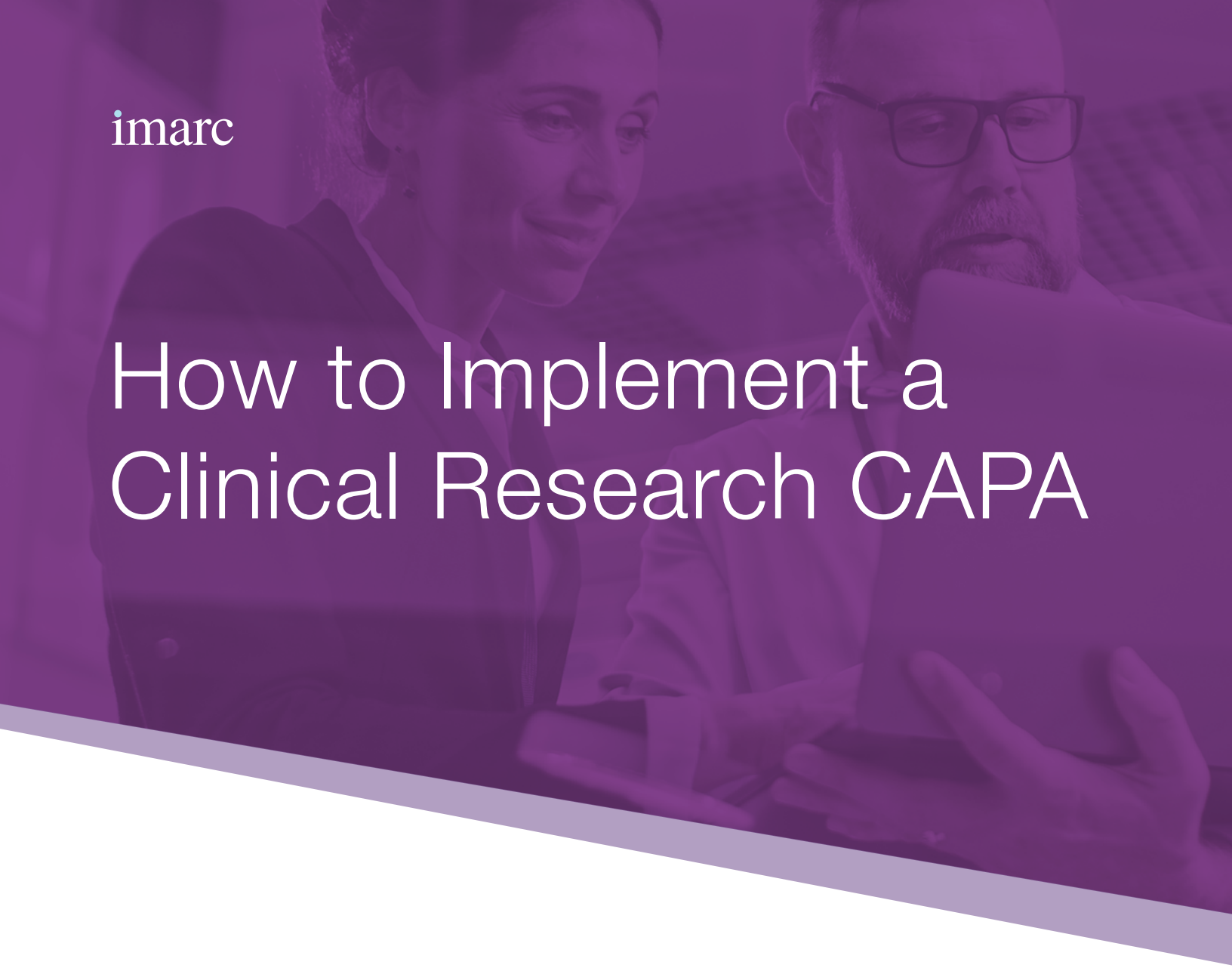

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How to Implement a Clinical Research CAPA

INTRODUCTION

What do swinging a baseball bat, shooting a basket, and throwing a football all have in common? Proper execution and follow-through can make all the difference. In clinical research, this analogy can be used for corrective and preventative action plan (CAPA) creation and implementation. Merely putting a CAPA in place is not sufficient when process level issues are noted. CAPAs must be properly implemented, verified, and closed.

Consider this case study:

Two devices are missing! At a routine monitoring visit, device accountability is performed to ensure that all investigational devices are accounted for and secure. After verifying all shipping, patient, and other records, the monitor confirms that the two devices should be on-site and not yet implanted into a study subject. And so the search of the hospital begins.

Are the devices in the cath lab? No.
Are they in the principal investigator's office? No.
Research offices? No.
How about the cafeteria? No.

After checking 17 other potential locations, the devices are nowhere to be found! What if the devices are never found? Or worse, could they have been implanted into non-study patients who did not provide informed consent?

A root cause analysis (RCA) and corrective and preventative action plan (CAPA) are completed. Luckily, the devices are located two months later in the department chair's office. Just four months after that, however, the same thing happens again. And this time one device is found to be implanted into a non-study patient.

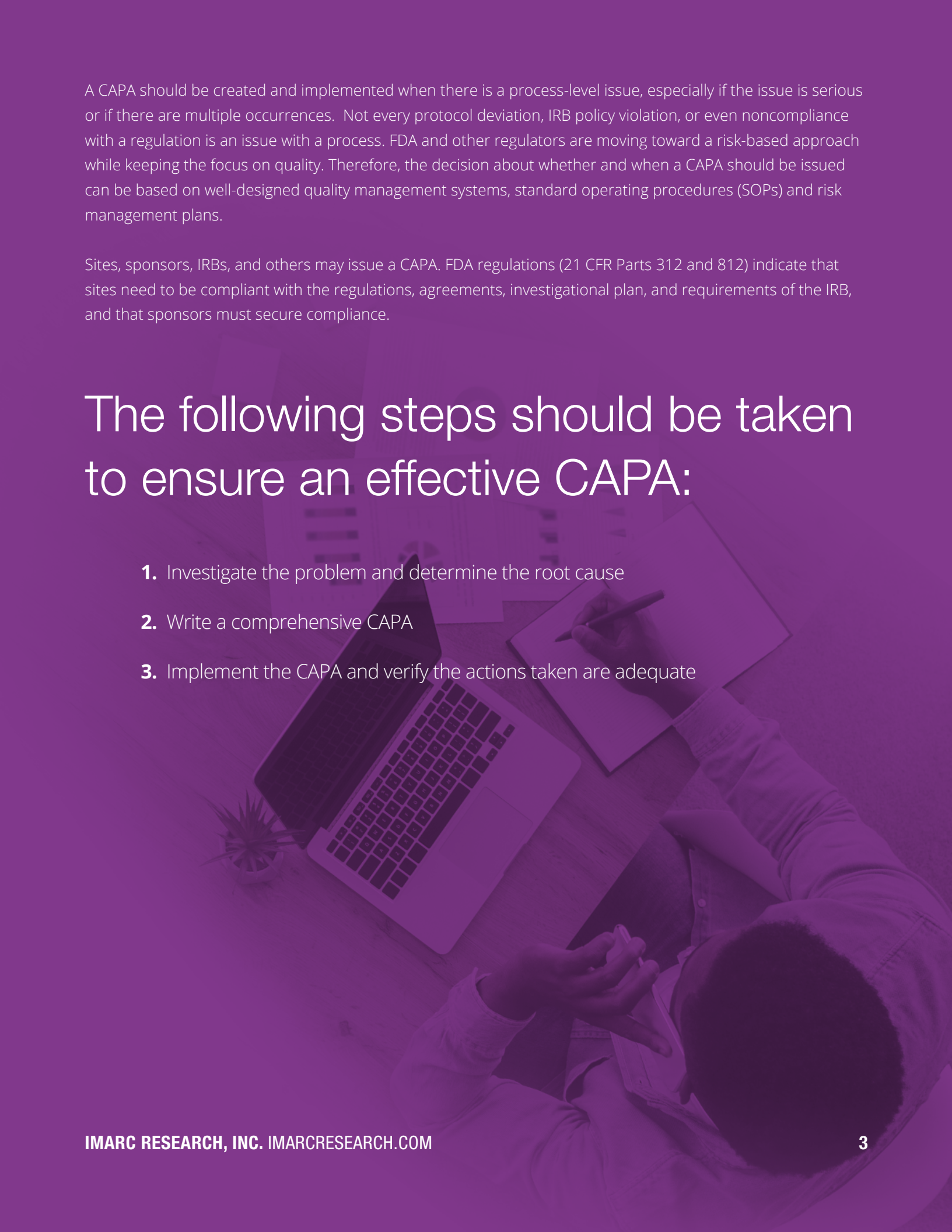
How could this have happened after a full investigation, root cause analysis, and the creation of a comprehensive CAPA?

A CAPA should be created and implemented when there is a process-level issue, especially if the issue is serious or if there are multiple occurrences. Not every protocol deviation, IRB policy violation, or even noncompliance with a regulation is an issue with a process. FDA and other regulators are moving toward a risk-based approach while keeping the focus on quality. Therefore, the decision about whether and when a CAPA should be issued can be based on well-designed quality management systems, standard operating procedures (SOPs) and risk management plans.

Sites, sponsors, IRBs, and others may issue a CAPA. FDA regulations (21 CFR Parts 312 and 812) indicate that sites need to be compliant with the regulations, agreements, investigational plan, and requirements of the IRB, and that sponsors must secure compliance.

The following steps should be taken to ensure an effective CAPA:

1. Investigate the problem and determine the root cause
2. Write a comprehensive CAPA
3. Implement the CAPA and verify the actions taken are adequate



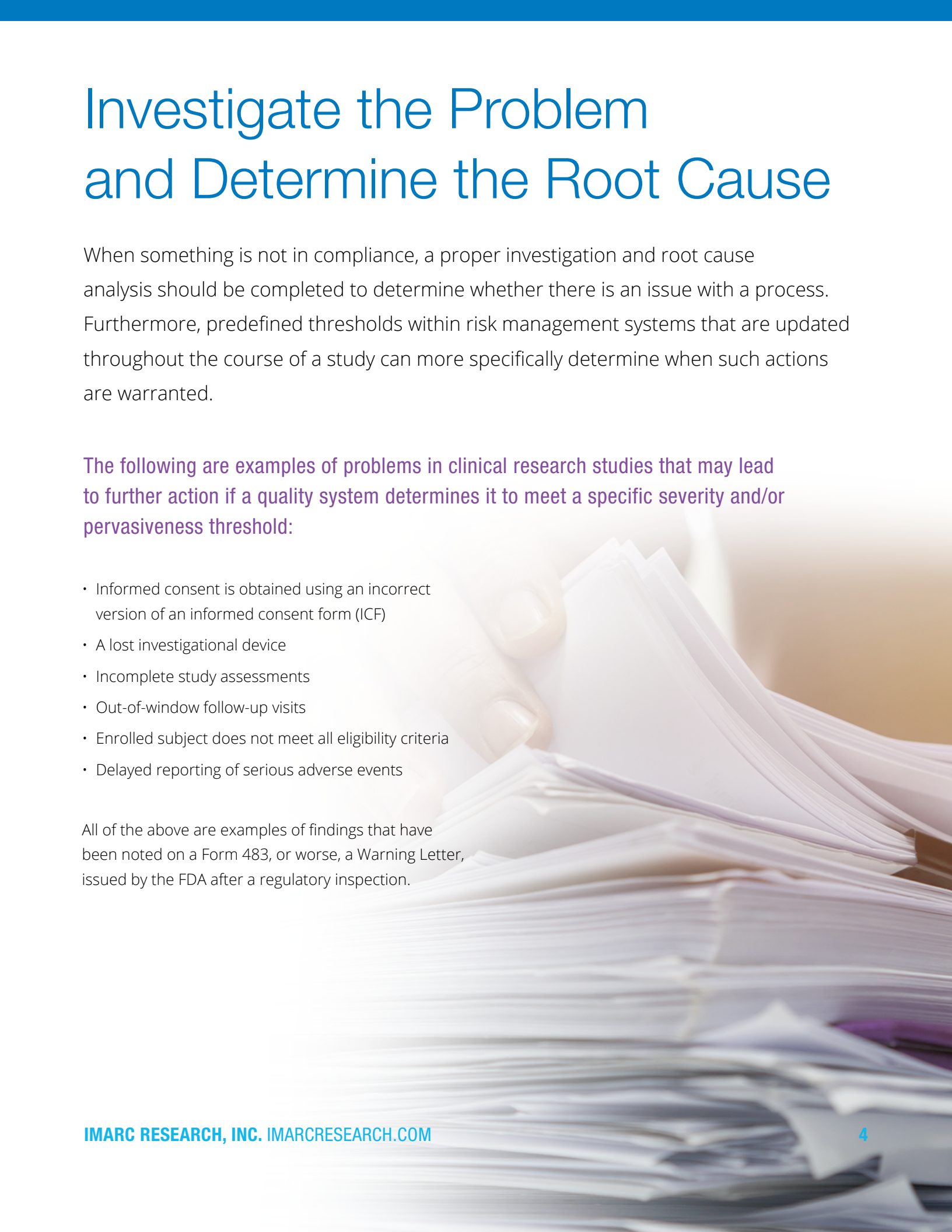
Investigate the Problem and Determine the Root Cause

When something is not in compliance, a proper investigation and root cause analysis should be completed to determine whether there is an issue with a process. Furthermore, predefined thresholds within risk management systems that are updated throughout the course of a study can more specifically determine when such actions are warranted.

The following are examples of problems in clinical research studies that may lead to further action if a quality system determines it to meet a specific severity and/or pervasiveness threshold:

- Informed consent is obtained using an incorrect version of an informed consent form (ICF)
- A lost investigational device
- Incomplete study assessments
- Out-of-window follow-up visits
- Enrolled subject does not meet all eligibility criteria
- Delayed reporting of serious adverse events

All of the above are examples of findings that have been noted on a Form 483, or worse, a Warning Letter, issued by the FDA after a regulatory inspection.



According to ISO 9001:2005, a root cause analysis (RCA) is a set of analyzing and problem-solving techniques targeted at identifying the actual root cause or the reason for the nonconformity. Without knowing why something happened, it would be very challenging to create an effective CAPA. Sponsors, CROs, sites and IRBs can initiate an RCA and also invite other parties to participate in the investigation.

There are several different RCA strategies available; for this discussion the Five Whys will be utilized. Members of the study team and possibly a representative from a quality assurance department should first investigate the issue and determine which RCA strategy is best for a specific problem. The Five Whys, for instance, asks why something occurred, then asks why again, and again, and again, until the underlying cause is identified.

For example, an RCA could be completed to determine why informed consent was obtained from five subjects using the previous version of an informed consent form:

Why did the subjects sign the previous version of the informed consent form?

Answer: There was a stack of previous versions in the research office.

Why was there was a stack of previous versions in the research office?

Answer: No one printed the new version and replaced the previous version.

Why did no one print the new version?

Answer: The research coordinator who had access to the IRB website containing newly approved informed consent forms was on vacation.

Why didn't someone else print the new informed consent form?

Answer: No one else had access to the IRB portal.

Why didn't anyone else have access to the IRB portal?

Answer: The site SOP specifies that one person on each study should be assigned the task of IRB correspondence in order to minimize redundancies and increase efficiency.

Therefore, the root cause was the SOP not allowing for a back-up staff member to have access to the IRB portal, so no one on the study team received a notification when a new informed consent form was approved. An issue with the process was clearly identified, so a CAPA is recommended. As is the case with anything in research, the investigation and RCA should be documented.

Write a Comprehensive CAPA

A well-written CAPA contains all the necessary details, yet it is also clear and concise. Details such as subject IDs, dates and protocol requirements should be included. The document should include enough context so that not only can study team members understand and follow its instructions, but monitors, auditors, regulators, and others can also review it months or even years later and verify that it was properly implemented.

While one person on the study team can be tasked with writing a CAPA, all stakeholders should partake in writing and reviewing the CAPA before it is implemented. For example, if the CAPA is used to resolve a nonconformance with a process at a site, a research coordinator can draft the document.

The following are examples of site personnel that should also review the CAPA and offer input: principal investigator, sub-investigators, other research coordinators on the team, research director, regulatory coordinator(s), and quality assurance personnel. Site personnel can also consult with the sponsor, monitor and/or IRBs.

These parties may provide in-depth assistance with drafting the CAPA, or at least review it before it is implemented. Meetings can be scheduled with sponsor and/or IRB personnel to brainstorm corrective and preventative actions.

Sponsors and IRBs can also initiate the CAPA process and may even require or recommend a specific CAPA template. Site SOPs, IRB policies, and sponsor requirements should be followed.

A well-written CAPA consists of the following sections:

1. **A brief summary** of the problem.
2. **A detailed narrative** of what occurred that includes subject ID(s), date(s) of occurrence, visits/assessments, that are affected, etc.

    a. **Reference** the applicable regulations, protocol requirements, IRB policies, SOPs, 1572 requirements and agreements that were not appropriately followed

    b. If applicable, explain how the issue did or could potentially affect **subject safety and/or the study data**

3. Summarize the **investigation and root cause analysis** strategy.
4. Describe the **root cause.**
5. List the **correction(s).** ISO 9000:2005(E) defines a correction as an action to eliminate a detected nonconformity. **How will the immediate problem be corrected?** Examples of corrections include:

    - Re-obtaining informed consent on the correct version of an ICF
    - Locating and securing the investigational product
    - Rescheduling a follow-up visit that was not completed
    - Reporting the problem to the sponsor and/or IRB according to sponsor and IRB requirements. The sponsor and IRB may provide further instructions.

6. List and explain the **corrective action(s).** ISO 9000:2005(E) defines corrective action as an action to eliminate the cause of a detected nonconformity or other undesirable situation. **What will prevent the problem from continuing or recurring?** Note that the appropriate actions will be dependent on the root cause and that multiple corrective actions may be needed. Examples of corrective actions include:

    - Informing and/or retraining current and new study personnel on SOPs, protocol requirements, informed consent process, etc.
    - Changing the storage area for the investigational product and implementing stricter access controls
    - Scheduling all follow-up visits as early as possible within the protocol required visit window
    - Reassigning the task of patient scheduling to a different person

7. List and explain the **preventative action(s).** ISO 9000:2005(E) defines preventative action as an action to eliminate the cause of a **potential** nonconformity or other undesirable situation. **What will minimize the potential for the problem to continue or be repeated?** Examples of preventative actions include:

    - Adding research coordinators to the study to provide additional support and implementing procedures to ensure that each study has enough personnel assigned
    - Adjusting the monitoring plan/strategy
    - A sponsor or monitor providing additional remote support
    - Modifying or updating an SOP to improve a process. For example, defining who is responsible for patient scheduling.

8. Describe the plan for **implementing, verifying, and closing** the CAPA. Additional information about these items will be explained in the next section.
9. Add the appropriate **signature lines.**

A CAPA must be documented, but there is no universal template. Sponsors, CROs, sites, IRBs, monitors, quality assurance departments or others may recommend or require that a specific template be used.

Here is an example CAPA template using the example of subjects that signed the previous version of an informed consent form:

Study: ProBleM Trial **Principal Investigator:** Dr. Kapa
Date Issued: 15 June 2020
Brief Description: Five subjects signed the previous version of the informed consent form

NARRATIVE

Subjects 500121 through 500125 signed the ICF approved by the IRB on 01 March 2020. However, a more current ICF had been approved on 01 April 2020, which was before the subjects signed the form. The new ICF contained the following new risk: ventral hernia. The study protocol and the IRB policy specify that all subjects must sign the most current ICF.

INVESTIGATIVE SUMMARY AND ROOT CAUSE ANALYSIS

The manager, quality assurance reviewed the informed consent documentation for the subjects above, and she also interviewed the PI and research coordinators to confirm what took place. The PI, research coordinators, and manager, quality assurance met on 12 June 2020 to complete a root cause analysis using the Five Whys Strategy.

ROOT CAUSE

The assigned research coordinator was on vacation when the IRB approved the 01 April 2020 consent form. The site SOP did not allow a back-up staff member to have access to the IRB portal, so no one on the study team received a notification when a new ICF was approved.

CORRECTION(S)

After consulting with the sponsor and IRB, it was determined that the above subjects should sign and date the most current ICF at the next follow-up visit. The research coordinator will explain the new risk to the subjects and document the discussion.

CORRECTIVE ACTIONS

Update the site SOP to specify that each study requires a minimum of two research staff members to have access to the IRB portal and receive notifications when new ICFs are approved. Provide IRB portal access to additional research staff. Train all applicable personnel on the updated policy.

PREVENTATIVE ACTIONS

Review the SOP annually and confirm if any processes should be updated. Add a requirement to the policy indicating that ICFs should not be printed until immediately prior to obtaining informed consent. Whomever will be obtaining consent should have access to the IRB portal and print the form directly from the portal. Train all applicable personnel on the updated policy and process for obtaining informed consent.

CAPA IMPLEMENTATION AND VERIFICATION PLAN

Additional information will be provided in the next section.

SIGNATURES

Principal Investigator:	_____	_____
	Printed Name	*Signature and Date*
Research Coordinator:	_____	_____
	Printed Name	*Signature and Date*
Manager, Quality Assurance:	_____	_____
	Printed Name	*Signature and Date*

Depending on the type and scope of the problem, other site personnel, sponsors, CROs, IRBs or others may sign the CAPA. Alternatively, CAPAs or certain portions of CAPAs can be documented using other methods such as monitoring reports/letters, IRB correspondence, sponsor-site communications, and protocol deviation forms.

Of note, while information about each specific protocol deviation could be documented on a form in an electronic data capture (EDC) system, additional documentation such as a CAPA form may be needed if there is a process level issue.

Implement the CAPA and Verify the Actions Taken Are Adequate

Completing a root cause analysis and drafting a CAPA is only the beginning. A CAPA cannot be effective if it is not properly implemented and the required actions are not verified. Otherwise, corrections may be incomplete and there is a higher likelihood of recurrence. Even worse, the problem would have the potential to grow further out of control.

Importantly, certain measures may need to be implemented immediately, even before the investigation and root cause analysis begin. For example, if several subjects were enrolled who did not meet all inclusion/exclusion criteria, a site, sponsor, and/or IRB should consider pausing or suspending enrollment until a CAPA is created and at least partially implemented. This type of immediate action prevents the problem from continuing before a CAPA is fully implemented.

Once the necessary immediate actions are taken and the CAPA is written, the following strategies can be considered for implementation.

Some or all of these may be documented within a section of the CAPA document:

- [ ] Once the CAPA is drafted, **share it** with the appropriate parties such as the sponsor, IRB, and monitor so that additional input can be provided. A meeting can be scheduled to review the CAPA and discuss the implementation and verification process.

- [ ] Schedule **CAPA training** with the appropriate personnel and document the training, particularly if the CAPA is complex or if the purpose is to resolve a serious problem. If needed, also arrange additional training on applicable regulations, GCP requirements, protocol requirements, IRB policies, etc. Furthermore, if new personnel are added to the study at a later date, those personnel can receive the same training.

- [ ] Although multiple personnel may be tasked with implementing and verifying the CAPA, it is recommended assigning one person as the **CAPA Coordinator**. This person can delegate tasks to others, but having one person responsible for carrying out the corrective and preventative actions can lessen the chance of something falling through the cracks. If the CAPA Coordinator leaves the study, then a replacement would be needed.

- [ ] Establish a **timeline** for each corrective and preventative action, and specify any ramifications for missed deadlines.

- [ ] Schedule **meetings and/or provide updates** to all those involved on a periodic basis and at necessary time-points. Information conveyed can include the current status of corrective and preventative actions, unanticipated hurdles, updates to the projected timeline, changes to the division of roles, and recommended changes to the implementation process.

- [ ] Determine a process for **amendments** to the CAPA and specify anticipated circumstances for when an amendment would be needed.

Assign someone the task of verifying that each corrective and preventative action has been properly implemented. **Verification has two components.**

First, each of the actions specified in the CAPA should be verified that they were completed appropriately.

Second, once some time has passed, three months perhaps, review the study documentation and/or interview applicable personnel to confirm that the corrective and preventative actions are working. The verification steps should be documented.

The following recommendations can take the place of all or some of the verification steps:

- **Adjust the monitoring** visit frequency, scope, or focus so that the implementation of the CAPA can be verified and additional support can be provided. Any observations and actions taken should be documented in a monitoring report and follow-up letter.

- **Schedule an audit** to ensure the CAPA was appropriately implemented and that it was effective. Sites and sponsors can schedule internal audits. Additionally, IRBs and sponsors can audit sites. An auditor can provide additional recommendations if any deficiencies are noted. Any findings and recommendations should be documented in an audit report.

Finally, the CAPA can be closed when all corrections, corrective actions, and preventative actions have been implemented and verified. A closing meeting may be scheduled to review all actions and confirm the problem has been fully resolved. All applicable personnel should sign the CAPA, and all documentation should be filed according to the appropriate SOPs.

Study-Wide CAPAs

CAPAs created and implemented by sponsors may apply to multiple sites within one study or to multiple studies. A project manager, someone from the sponsor's quality assurance department, or other team member may take the lead in creating and implementing the CAPA. Like CAPAs at the site level, however, all appropriate personnel should participate in the process.

Here is an example of an issue that could occur across multiple sites within one study and a CAPA that can be created to address it:

Sponsor: Risky Device, Inc. **Study:** ProBleM Trial
Date Issued: 20 June 2020
Brief Description: 35% of ultrasound images did not capture all required vein segments

NARRATIVE

The protocol requires bilateral ultrasound assessments of the common iliac vein, external iliac vein, and common femoral vein at each follow-up visit. The following ultrasound assessments did not capture the left common iliac vein:

- Subject 051002: three-month follow-up assessment on 01MAR2020
- Subject 065007: 12-month follow-up assessment on 06MAR2020
- *(Note: additional assessments would be listed here)*

The following ultrasound assessments did not capture the right common iliac vein:

- Subject 065007: 12-month follow-up assessment on 06MAR2020
- *(Note: additional assessments would be listed here)*

INVESTIGATIVE SUMMARY AND ROOT CAUSE ANALYSIS

The project manager, imaging specialist and CRAs reviewed study documentation including submitted data and imaging, monitoring reports, and site communications. Additionally, study team members spoke with six sites to further understand the challenges with collecting imaging. Afterwards, the study team met on 15 June 2020 to complete a root cause analysis using the Five Whys Strategy.

ROOT CAUSE

The ultrasound assessment instructions were not properly communicated from the research staff to the ultrasound technicians because insufficient guidance on the ultrasound requirements was provided by the sponsor.

CORRECTION(S)

The project manager and CRAs will work with sites to ask all subjects who had an incomplete assessment to return to the site for a repeat assessment if it can be repeated within the visit window or up to three months after the end of the window. Sites will be instructed to notify the IRB and ask if subjects need to sign a new ICF for the repeat assessment. Any IRB requirements should be followed. Discussions with the subjects about the risks and benefits of the repeat assessment should be documented.

CORRECTIVE ACTIONS

The project manager, CRAs, and imaging specialists will re-train all PIs and research coordinators on the imaging requirements and offer additional guidance during the training. A communication tool and checklist will be drafted and sent to all sites in order to help ensure the appropriate instructions are communicated to the ultrasound technicians. CRAs will send written reminders to sites prior to each upcoming ultrasound assessment and include the necessary instructions.

PREVENTATIVE ACTIONS

All ultrasound technicians who assess study subjects will be required to complete training on the imaging requirements defined in the protocol and imaging materials. Training will be documented. A new study task, "Ultrasound Assessments," will be added to the Delegation of Responsibilities Log, and the PI will need to delegate this task to any technician who will assess a study subject. Additionally, sites will be required to submit imaging to the core lab within two business days of the assessment, and the core lab will be required to provide quality feedback to the site within one business day after receiving the image. If a site completes one additional incomplete assessment, then an on-site meeting and training will be scheduled. Finally, study training plans will be updated to require training for ultrasound technicians.

CAPA IMPLEMENTATION AND VERIFICATION PLAN

The project manager will be the CAPA Coordinator and oversee the implementation. All CRAs and imaging specialists will be trained on the CAPA requirements by the end of June. All ultrasound technicians will be trained via web training by July 15th. This CAPA will be a standing agenda item during biweekly study meetings until the CAPA is closed, and any needed amendments can be proposed during these meetings. The imaging specialists will review all imaging on a weekly basis to monitor improvement.

During monitoring visits the CRAs will review ultrasound technician training records and communications between the research coordinators and technicians. Monitoring visit frequency will be increased at sites with a lower rates of compliance with the imaging requirements. In September 2020, audits will be scheduled at the three sites with the lowest rates of compliance with the imaging requirements, and the auditors will be directed to review the ultrasound documentation and process.

SIGNATURES

Principal Investigator: _____ _____

Printed Name *Signature and Date*

Research Coordinator: _____ _____

Printed Name *Signature and Date*

Manager,
Quality Assurance: _____ _____

Printed Name *Signature and Date*

Although creating and implementing CAPAs may appear daunting at first, the process usually isn't too time intensive, especially after a little experience is gained. CAPAs that are implemented successfully can resolve process-level problems that may cause potential harm to research subjects and/or decrease data quality.

Regulators are moving increasingly towards a risk-based and quality approach to clinical studies. Therefore, CAPAs have become the norm for process-level problems. Lower rates of compliance can result in findings at a regulatory inspection, but providing an auditor with documentation of efforts to increase compliance may either decrease the severity of the findings or potentially result in no findings.

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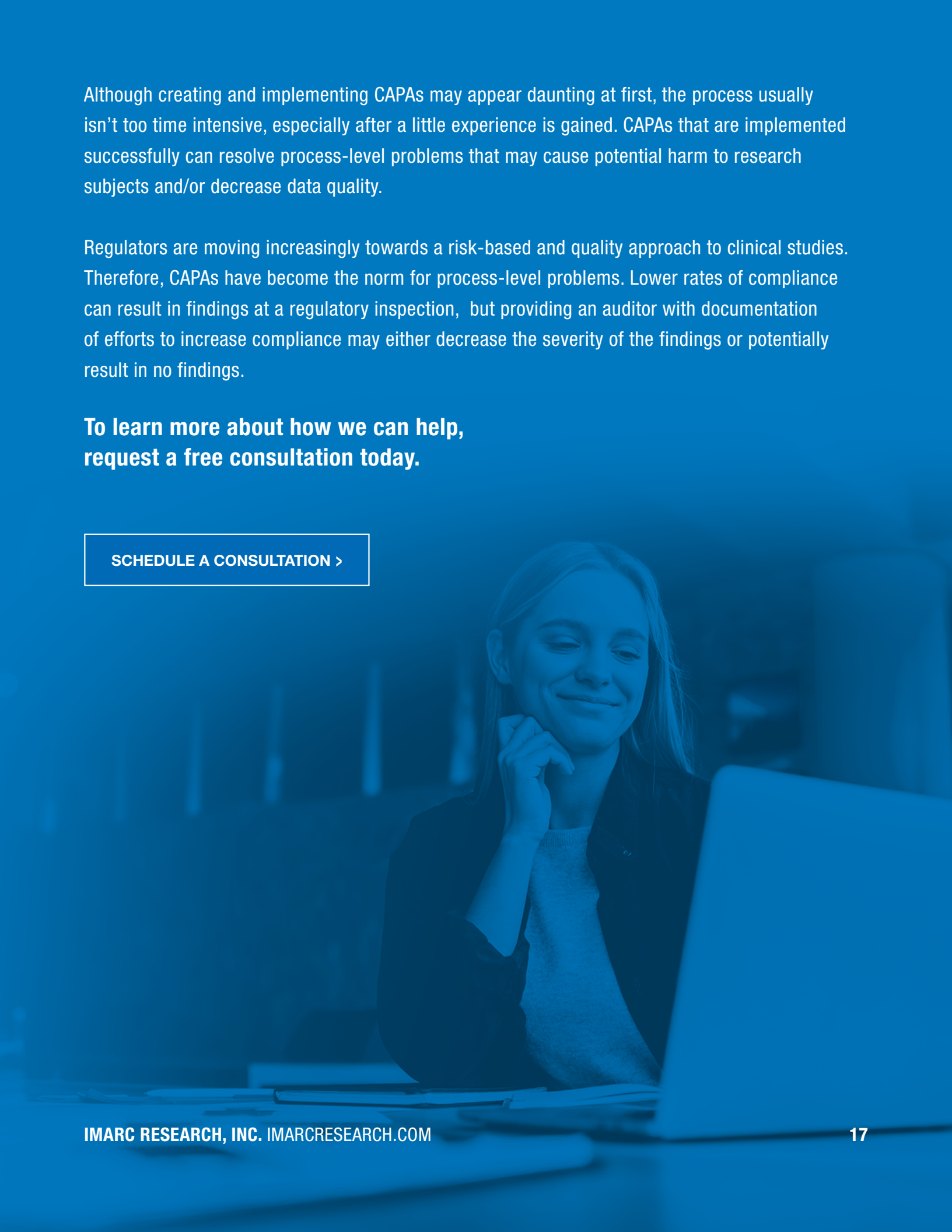

Bradley Lieberman, Manager, Monitoring Services

Bradley is currently the manager of monitoring services at IMARC Research, Inc., a medical device CRO. He was previously a Lead CRA and CRA at IMARC and monitored the following therapeutic areas: cardiovascular, neurology, surgery, and GI. Prior to that, he was an internal CRA at AtCor Medical, a company that specializes in central blood pressure and arterial stiffness products. Brad received a bachelor's degree in neuroscience from the University of Michigan.

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