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Giving Your Studies a

fair((shake))™

A 4-Point Guideline to Navigate Through Regulations

I have a confession to make. I was a clinical research coordinator for 2 years before I ever read one regulation. That's a fact. I screened, recruited, and consented subjects, recorded data, maintained drugs and devices, and followed subjects in clinical research studies without ever reading one regulation that governed the clinical research industry. To be honest, I don't even remember knowing that there were regulations that governed clinical research, and yet, I played a key role in the partnership with human subjects, the very people for which the regulations were created to protect.

If you were to ask me at that time if I intended to violate any regulations pertaining to human subject protection, I would have been offended by the question. Ask me now and I would probably utter something like "ignorance was bliss." Being ignorant to the requirements of human subject protection caused me to conduct myself with proverbial blinders on, unable to recognize a non-compliance when I saw it, or worse yet, when I was committing one. Since reading - and eventually being able to apply - the regulations, I have developed a new respect for and understanding of how even seemingly innocent actions, or inactions, have the potential to negatively impact human subjects.

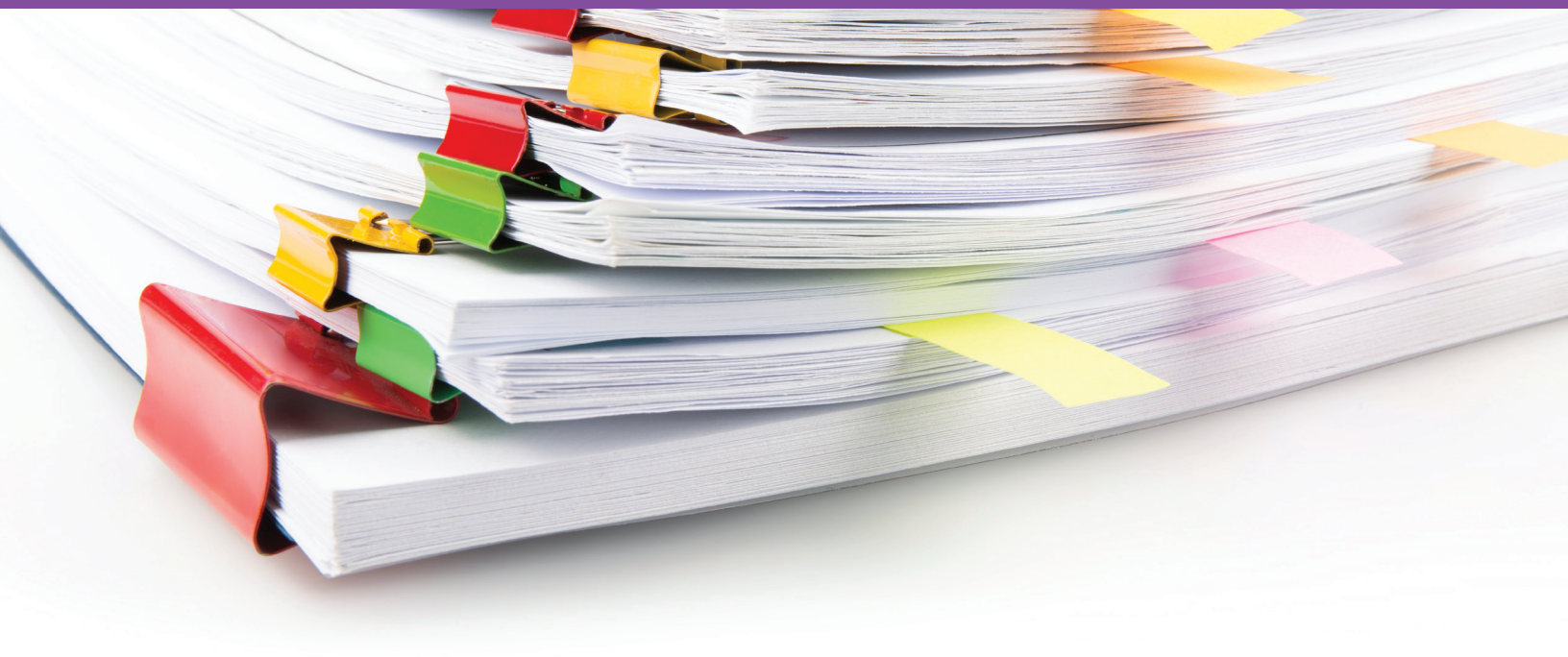
I've now been in the clinical research industry for 15 years, and what I'm finding is that my story is not unusual. When I conduct informal polls of clinical research professionals regarding their training, most indicate that they were trained "on the job" by shadowing a colleague for a number of days or weeks, or they are "thrown in" and rely on monitors to teach them the ropes. Most of them share that they never had any formal good clinical practice training prior to assuming study responsibilities, and if they did receive it, they did not necessarily understand its relevance to their daily tasks.

HAVING SAID THAT, THERE HAVE BEEN SOME

GREAT IMPROVEMENTS ON THE CLINICAL RESEARCH EDUCATION FRONT

IN THE LAST DECADE, INCLUDING:

- **There are now several professional organizations that host conferences each year devoted to the topics of partnerships with human subjects;**
- **Masters level programs devoted to research administration are popping up at various universities;**
- **Nursing programs are including hands-on research education as part of their clinical programs;**
- **Some IRBs are requiring basic GCP training before study staff can work on a clinical trial;**
- **Sponsors are starting to provide sites with GCP training prior to initiating a trial;**
- **Various organizations are providing certification as a means to establish minimum competency in the field;**
- **Government organizations are providing free online tutorials for clinical research professionals.**



But even with that, we're still falling short.

Perhaps still under the shelter of "ignorance," we, as an industry, continue to routinely violate regulations as evidenced by a continuous stream of warning letters flowing out of the various offices of the FDA. While we may be getting better at knowing what we need to know, we are still struggling with application. Instead of basing our decisions in the regulations, we routinely base them on what the person who sits in the cubicle next to us thinks, what our monitor thinks, what the investigator thinks, or "this is how we've always done it."

The goal of this white paper is to introduce you to the concept of the FAIR Shake™ in an effort to foster a pattern of thinking that will allow you to navigate through the complexity of the regulatory framework in a very simple way that is based in regulatory fact as opposed to popular opinion. The FAIR Shake™ technique takes an otherwise complicated maze of requirements and breaks them down into four simple areas that can be applied to clinical research questions. Using this technique will position you to raise the bar on your own study teams as you gain confidence in your ability to wage an educated debate when potential areas of non-compliance are raised.

The foundation for the FAIR Shake™ technique for device studies is based in 21 CFR 812.110 which states, "An investigator shall conduct an investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part, and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA." In addition, for drug studies, 21 CFR 312.60 indicates that "An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations..." and then goes on to explain their requirements with complying with IRB regulations in 21 CFR Part 56.

In essence, both drug and device research boil down to four main areas of regulatory compliance. It is important to note that of these four areas, some are fixed and some are variable:

F	Federal regulations	Fixed
A	Agreements (FDA Form 1572 - drugs / Investigator Agreements - devices)	Fixed for drugs; variable for device
I	Investigational Plan (protocol)	Variable
R	Requirements of the IRB	Variable

- Regulations are fixed. They are non-negotiable. They are not suggestions. For industry-sponsored drug and device research studies, the following regulations should be on your "must read" list:
  - **21 CFR 11**: Electronic records
  - **21 CFR 50**: Protection of human subjects
  - **21 CFR 54**: Financial disclosure by clinical investigators
  - **21 CFR 56**: Institutional review boards
  - **21 CFR 312**: Investigational new drugs
  - **21 CFR 812**: Investigational device exemptions

- Agreements are fixed for drug studies but are variable for device studies. To participate in a drug study, investigators must sign a "Statement of Investigator" or Form FDA 1572. For device studies, agreements are negotiated on a project by project basis and are variable.

- Investigational plans are certainly variable, with differences in protocol design, populations to be studied, eligibility criteria, procedural requirements, randomization procedures, and follow-up requirements to name a few.

- Requirements of the IRB vary in terms of general procedures, informed consent policies, adverse event reporting policies, protocol deviation requirements, and other IRB-specific expectations.

So because some elements of the FAIR Shake™ are variable, the key to "application" lies in understanding the following:

A decision about regulatory compliance made at one site for one study may not be the right decision at another site for the same study or at the same site for another study.

In other words, just because you navigated your way through the maze with a correct answer for Study A, the same situation that presents itself for Study B may have a different answer. Or if Study A is being run at multiple sites, it is very possible that the correct answer for Site 1 is not the correct answer for Site 2. Why? Because the agreements may be different, because the investigational plans may be different, and because the requirements of the IRBs may be different. I encourage you to sit with that until it makes sense.

So keep it simple! When faced with a decision about regulatory compliance, ask yourself the following questions:

F	Federal regulations • Is it specified in 21 CFR Parts 11, 50, 54, 56, 312, or 812?
A	Agreements • Is it a requirement in the Agreement?
I	Investigational Plan (protocol) • Is it a requirement in the investigational plan (protocol)?
R	Requirements of the IRB • Is it a requirement of the IRB?

Here is a light-hearted example question to illustrate this point:

> My monitor tells me that I have to use blue pen to complete my data forms. She says "It's in the regs..." Do I really have to do that?

GIVING THIS QUESTION A FAIR ((SHAKE))™		IS IT "IN THE REGS?"
F	It is not a line item in 21 CFR Parts 11, 50, 54, 56, 312, or 812.	NO for drugs NO for devices
A	It is not in the Form 1572 for drug studies; It could potentially be in the Agreement for a device study.	NO for drugs POSSIBLY for devices
I	It is possible that the protocol contains information about how data will be gathered and recorded, including a requirement to use blue pen.	POSSIBLY for drugs POSSIBLY for devices
R	It is unlikely that IRBs would require a certain color of pen being used to record data.	NO for drugs NO for devices

In the scenario above, it is possible to answer "Yes, it's in the regs" as well as "No, it's not in the regs" based on the variable factors. While using a blue pen is not a line item in the regulations, it could possibly be specified in a device agreement or in the protocol. If it is specified in either of those two documents, then using blue pen becomes a federal regulation. While that in and of itself sounds silly and probably would not warrant a citation on a warning letter, the regulations require that the investigator comply with the agreement and the investigational plan, so failure to do so would be a violation of the federal regulations.

Here is a more relevant example to further illustrate this point:

> The investigator of a device study routinely signs the consent forms days after the patient signs them. A monitor visits you and tells you that this practice must stop immediately as it is a violation of federal regulations. Is it?

GIVING THIS QUESTION A FAIR ((SHAKE))™		IS IT "IN THE REGS?"
F	It is not in 21 CFR Parts 11, 50, 54, 56, 312, or 812. Of note, 21 CFR Part 50.27 requires that the informed consent be signed and dated by the subject, but does not address the need for the investigator to sign the document.	NO for drugs NO for devices
A	It is not in the Form 1572 for drug studies; It is most likely not contained in the Agreement for a device study.	NO for drugs NO for devices
I	It is most likely not contained in the investigational plan.	NO for drugs NO for devices
R	This very possibly may be a requirement of the IRB. In addition to finding out if the investigator's signature is required, it would be important to know what the meaning of that signature is. Is it to act as a witness? Is it to affirm that the study was explained to the patient? Those are two different scenarios that might result in two different answers to the question above. Seeking clarification from the IRB would be essential to answering this question.	POSSIBLY for drugs POSSIBLY for devices

In the example above, if the investigator is required by the IRB to sign the consent form in a certain period of time relative to consenting, and she has not done that, then she is in violation of 21 CFR 812.110 which requires investigators to comply with their IRB. Thus, even though an investigator signature is not a line item requirement in the regulations, by default, in this case, it becomes a federal regulation due to the fact that the IRB requires it.

The regulations that govern clinical research are there for a very important reason

- to protect the human subjects that are on the other side of that consent form, the human subjects that together make up that target enrollment number sites strive to reach, the human subjects whose stories are told inside all of those binders. As clinical research professionals, it is our responsibility to not only know the regulations, but to know how to apply them in various situations. Training is essential. Accurate application is essential. Adopting this FAIR Shake™ technique into your daily practice will help you bridge the two. Learn from my mistakes - instead of passing the blinders around, commit to taking them off and throwing them out.

Sandra Maddock CEO and President

Under Sandra Maddock's leadership, IMARC Research was founded in 1999 to deliver the highest-quality clinical research monitoring, auditing, training/development and consulting services.

Sandra offers IMARC partners years of expertise covering:
coronary and peripheral stents, angioplasty balloons, combination products, thrombolytics, chemotherapy agents, endovascular grafts for treatment of thoracic and abdominal aortic aneurysms, wound care, and dura mater replacement grafts. Whether serving as a global auditor for a device study across the U.S., Japan and Germany, or working with U.S. sites establishing GCP Compliance in preparation for an FDA Inspection, Sandra's hands-on approach has become her trademark.

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.