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Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

April 2019 (Volume 33, Issue 4)

The Nuts and Bolts of Clinical Trials

Clinical Researcher™

Association of Clinical Research Professionals

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Table of Contents

4 Executive Director's Message—Let's Keep the Conversation Going
Jim Kremidas

PEER REVIEWED

6 An Overview of the Prospects for Using Wearables to Improve Clinical Trials
Geoffrey Gill, MS

13 Revisiting the Form FDA 1572

COLUMNS

22 Clin Ops Insights—Why a Well-Planned Protocol Authoring Process is Critical for Successful Research
Priti Sahai, MBBS, MS

26 PI Corner—Taking the First Steps on the Path to Being a PI
Elizabeth Weeks-Rowe, LVN, CCRA

SPECIAL ADVERTISING SUPPLEMENT

30 Frenova Renal Research—The Burden of Research on Physician Practices: Is Relief in Sight?
Kurt Mussina

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Clinical Researcher—April 2019 (Volume 33, Issue 4)

EXECUTIVE DIRECTOR'S MESSAGE

Let's Keep the Conversation Going

Jim Kremidas

I attend a lot of conferences. Like many of you, I enjoy the opportunity to reconnect with other professionals, colleagues, and friends to swap ideas and commiserate about the frenzied pace of change in the clinical trial industry.

I mention this because we've just wrapped up another successful ACRP annual conference. The ACRP 2019 gathering delivered some excellent speakers, thought-provoking panels, and a lot of fun at the Music City Center in Nashville, Tenn. However, I noticed something special this year I wanted to share with you. Whether it was during a Q&A or in a networking break, I had several people tell me they had changed specific ways of doing things because of what they'd learned at sessions last year. In several instances, attendees told me this year they had texted someone back in the home office *during* a session to find out if it was time to make a change based on what a session speaker was sharing.

Talk about actionable intelligence!

Conferences are a great way to inspire us to do even better work. They are invaluable when it comes to helping us better understand new rules and guidances by having direct access to regulatory officials. They are also a way to pay it forward by sharing your own knowledge with others.

That said, I can't think of the last conference I attended where participants were using and sharing information gleaned at a session so quickly and tangibly as what I witnessed in Nashville earlier this month. Let's keep the conversation going. We appreciate your feedback on how the event went (if you were there) and—based on any of our gatherings you have ever attended—on how we can do even better next year in Seattle.

We enjoy the opportunity to come face-to-face with so many members, volunteers, exhibitors, and partners at our annual meetings. We are extremely grateful for your support. Now that the ACRP staff have returned to their offices and begun to catch up on the more typical day-to-day work of the Association, I hope you'll stay engaged with us by finding "news you can use" in this and every issue of *Clinical Researcher* and in our weekly e-newsletter, the *CRbeat*.

At ACRP, we're committed to providing you with the most valuable data and information possible to help you do even better work in the challenging world of clinical trials. As always, I welcome your thoughts about how we can help support our shared mission of getting treatments to patients as safely and efficiently as possible.

Jim Kremidas (jkremidas@acprnet.org) is Executive Director of ACRP.

Clinical Researcher—April 2019 (Volume 33, Issue 4)

PEER REVIEWED

An Overview of the Prospects for Using Wearables to Improve Clinical Trials

Geoffrey Gill, MS

Drug development costs today have spiraled out of control. A report from Tufts in 2016{1} estimated the cost of introducing a new drug at $2.6 billion. On the other side, a 2018 report from Deloitte{2} estimated that the return on investment for new drug development had dropped from 10.1% in 2010 to 1.9%. Clinical trials are the key driver of cost and return, not only because they are very expensive to conduct, but also because their results are not always accurate—causing pharmaceutical companies to invest in late-stage clinical trials for drugs that never get to market or are not sufficiently differentiated to capture high returns if they do get to market.

Wearables are a key feature of one of the few promising approaches for revolutionizing clinical trials and addressing these issues. The reality is that most approaches to improve clinical trials are designed to make the existing processes more efficient, but wearables can fundamentally improve how outcomes are measured by providing a continuous stream of objective data. Furthermore, these data are consistent across geographies and can be available in near real time, allowing for compliance monitoring and management in a timely fashion.

These factors are becoming increasingly important as trials become more global. Current measures like patient-reported outcomes or in-clinic tests are often subjective, sporadic, variable across regions, and prone to inaccuracies, which can lead to faulty conclusions. By changing the outcome measures, wearables are moving the goal posts and providing the potential for significantly reduced sample sizes, shortened trials, and better clinical data to differentiate the drug.

Regulatory Support

If wearables can solve all these problems, why are they currently used in less than 1% of trials?{3} The issue is not U.S. Food and Drug Administration (FDA) approval; the FDA has provided strong indications that it supports the use of real-world data. FDA Commissioner Dr. Scott Gottlieb has stated that leveraging real-world data to improve regulatory decisions is a key strategic priority for the FDA. In December 2018, the FDA also introduced a new strategic framework to advance use of real-world evidence to support development of drugs and biologics.{4}

It is also pretty clear that wearables do not need to be approved as a medical device to be used in a trial. The *Clinical Trials Transformation Initiative (CTTI) Recommendations: Advancing the Use of Mobile Technologies for Data Capture & Improved Clinical Trials* explicitly state that "Mobile technologies for data capture in clinical trials do not typically need to be approved or cleared as a medical device."{5} Furthermore, wearable devices from several companies, including Actigraph, MC10, AliveCor, and Apple have received FDA approval and been used in clinical trials. However, FDA approval of a wearable as a medical device does not necessarily translate to FDA acceptance of use of the metrics it generates to define an endpoint.

Wearables Challenges

Most of the wearables on the market today have their own proprietary algorithms with no clinical validation or access to the raw data on which they were based, making the use of these data problematic. Proving to the FDA that a clinical trial is measuring real-world data that correspond to patient outcomes is difficult or impossible without raw data. Furthermore, without raw data, analyses cannot be upgraded as new algorithms are validated. There is no way to determine whether an anomalous reading is real or indicative of an issue. Without raw data, there is no way to build a real knowledge base that can be used going forward.

Then there is the challenge of including another technology in the trial—sites and participants are already overburdened, and asking participants to remember to charge a device or manage uploads or wear a bulky and/or uncomfortable wearable will often result in compliance issues, creating a whole new failure mode for the trials. Relying on the sites to manage this process will be costly and further stretch resources.

Running clinical trials is already difficult and expensive. Adding another element increases effort, cost, and the risk of failure—even if it is relatively easy to manage. No wonder the penetration of wearables in clinical trials is so low.

Still, something must be done to address this challenge, because wearables represent one of the best opportunities to truly revolutionize the clinical trials industry. Some sponsors hope that wearables companies will address all of these issues alone, but as a matter of economics, that is unlikely to happen—there are literally thousands of potential applications for wearables in clinical trials.

For example, they can be used to study a broad range of complex musculoskeletal or neurological conditions, such as Alzheimer's disease, Parkinson's disease, epilepsy, and cancer. The cost of developing and validating algorithms for all these applications is prohibitive, especially since the market for wearables for clinical trials is relatively small and low margin. To put this in perspective, my firm projects that the total potential market for wearables in clinical trials will be approximately $1 billion annually, which is less than half the cost of bringing one

drug to market. It is unrealistic to expect the wearables industry to make the investments necessary if the pharmaceutical industry won't.

Wearables Opportunities

Still, there is hope. The pharmaceutical industry can leverage years of work and experience garnered from using wearable sensors in other fields, particularly in academic and consumer neuroscience settings.

Many academic researchers are using wearables to conduct studies that could be relevant for clinical trials. For example, researchers at Boston University are currently using wearable sensors to study the effect of physical activity on cognition. Participants undergo a battery of cognitive tests at the start of the study and then their activity is monitored during waking hours for the next 12 weeks using a wearable device that collects all of the raw accelerometer data. Fifty percent of the participants are encouraged to exercise with weekly "coaching calls" and other methods; the remainder receive no additional assistance. At the end of the study, participants undergo a second battery of cognitive tests. If this study produces positive results, it will provide validation that improving activity levels will help improve cognitive results, enabling a potential outcome measure using wearables.

This type of work is being done by literally thousands of researchers around the world. In many, if not most, cases the algorithms are publicly available and independently verified. For example, there is a public domain activity and sleep algorithm based on accelerometry, GGIR,{6,7} that has more than 80 peer-reviewed articles that rely on the method.{8} Although not all academic research is so well documented and validated, much work has been done and it provides a major platform on which to build validated metrics. Leveraging this invaluable resource will require both access to the raw data and transparency on the part of the wearable supplier.

Experiences from consumer neuroscience (sometimes called neuromarketing) can teach us a great deal about developing scalable systems for collecting data. Neuroscience studies need to be completed in days or weeks, not months, at a fraction of the cost of a clinical trial. In one example, a company incorporated wearable sensors into market research kiosks in six malls and movie theaters around the country. This approach enabled nontechnical staff to collect about 15

minutes of medical quality electrocardiograph and galvanic skin response data from participants while they were viewing content specifically selected for the individual. The raw data were sent automatically to a central server for analysis. If certain sites were not meeting their quota for participants, that quota could be reallocated to other sites in real time. That system could collect data from 1,000 people in a weekend, at a cost of less than $50 per participant.

Another opportunity to address these challenges is for pharmaceutical companies to collaborate on algorithm development and agree on appropriate industry outcome measures. Although intellectual property is generally highly valued in the pharmaceutical arena, these algorithms and outcome measures could be cooperatively developed in a precompetitive environment; all companies would benefit from these improvements. There is a growing movement in the industry in this direction and it should be encouraged as much as possible.

Pharmaceutical companies will need to partner with wearables companies. Wearables companies will not be able to accomplish these goals on their own.

Assessing Partnership Potential

There are a several important attributes that pharmaceutical companies should look for in a wearables partner. First, it's critical that they gain access to the raw sensor data; without those data, it will be impossible to move forward on a larger scale. Algorithms from academic studies and other pharma companies will depend on it, as will continued progress.

Second, the data need to be collected as completely as possible. To meet this challenge, the sensors and systems must encourage compliance by putting the minimum burden on participants and sites. The system should have robust tracking features to allow the sponsor or contract research organization to monitor trial progress and take corrective action as issues arise. The system should also include multiple failsafe mechanisms to prevent data loss at all stages of data capture.

Third, the wearables company should be committed to openness and industry collaboration. It will be difficult, if not impossible, for proprietary algorithms to be accepted as validated outcome measures. Even if they are accepted for a specific application, they will not be able to be

extended by the industry. Although it may be difficult for some companies to accept, the wearables industry will need to compete on other dimensions if the use of wearables in clinical trials is to grow.

Finally, pharmaceutical companies should also seek wearables companies who have an extendible platform. A single partner enables more efficient implementation of different sensors into a company's systems, but more importantly, it takes time, effort, and trust to build a productive collaborative relationship. It is difficult to achieve that with many different partners.

Conclusion

There are many challenges to improving clinical trials through the use of wearables, but by leveraging work done in academia and other industries and taking a collaborative approach, they can play a role in fueling the industry's goals of getting better drugs to market cheaper and faster. In the end, that is what it is all about.

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8. See https://github.com/wadpac/GGIR/wiki/Publication-list for a list of references.

Geoffrey Gill, MS, is President of Shimmer Americas, leading the U.S. operations and the commercial efforts for North and South America for Shimmer Research, a designer and manufacturer of medical grade wearables.

Clinical Researcher—April 2019 (Volume 33, Issue 4)

PEER REVIEWED

Revisiting the Form FDA 1572

The U.S. Food and Drug Administration's (FDA's) Form FDA 1572 is one of the many important regulatory documents submitted to the agency in connection with clinical trials. Many common mistakes are made when filling out and maintaining the 1572 form, so the hope is this guide will be useful to new sites, clinical research coordinators (CRCs), clinical research associates (CRAs), and other clinical research professionals.

This guide serves as a quick read in very simplistic and clear language that defines what a 1572 is, what a principal investigator (PI) is committing to when signing this document, how to fill it out, how to avoid common mistakes, and how to maintain it for the duration of the study. In addition, this guide offers a detailed look at each section of the document.

What is the Form FDA 1572 (Statement of Investigator)?

The Statement of Investigator (Form FDA 1572) is a form that is required to be filled for clinical trials involving investigational drugs or biologics. Through this form, the PI provides specific information to the sponsor, including his/her qualifications and information about the clinical site, in aim of assuring conduct of the clinical trial according to FDA regulations and guidelines.{1} By signing the 1572 form, the PI is making a legal commitment to adhere to FDA expectations by:

1. Agreeing to supervise or conduct the investigational trial according to the current study protocol. No changes are to be made to the study protocol without the sponsor's and institutional review board's (IRB's) acknowledgment and approval, unless it was mandatory for the purposes of protection and safety of the subjects.
2. Assuring his/her understanding of the study protocol and investigational brochure, including the potential side effects associated with the investigational product and his/her responsibility to ensure that all study personal involved in the conduct of the trial understand their responsibilities and duties.
3. Reporting all adverse events and serious adverse events to the sponsor that occur during the conduct of the trial in accordance with Title 21 CFR 312.68 in the *Code of Federal Regulations.*
4. Agreeing to obtain an informed consent form (ICF) from each participant by using the most up-to-date and IRB- and sponsor-approved ICF in accordance with Title 21 CFR part 50.
5. Agreeing to maintain adequate and accurate records and having them available for inspections in accordance with Title 21 CFR 312.62 and 312.68.
6. Agreeing to comply with all other requirements regarding the obligation of clinical investigations and all other pertinent requirements in accordance with title 21 CFR part 312.
7. Agreeing to oversight from an IRB that complies with all the requirements of title 21 CFR Part 56 and will be responsible for receiving and approving of the clinical investigation from beginning of the study until closeout. By this, he/she also agrees to report promptly any changes in the research activity, including any unanticipated problems involving risks to human subjects.{2}

When Must the Form FDA 1572 be Signed?

According to U.S. regulations, the Form FDA 1572 is required to be collected from all PIs for studies being conducted under an Investigational New Drug (IND) application, which would include clinical studies of an investigational product or biologic, excluding device-related clinical trials (which require a similar form called an "investigator agreement" to be filled out under an Investigational Device Exemption application.{1}

When Must the Form be Updated or a New One Completed?

- In cases when a new site is added or of replacement of an investigator at an existing site, a 1572 must be submitted to the FDA within a 30-day window of the site's/investigator's addition/replacement.
- Another case when a 1572 should be updated is when any site information is changed, such as the IRB or laboratory affiliated with that site.{3}
- Most sponsors require that if the PI listed in the current 1572 has his/her name changed for any reason (e.g., marital status), the document should be updated. If a sub-investigator has a name change, then in most cases sponsors ask for the form to be updated or a note to file provided explaining the name discrepancy from an audit and Good Clinical Practice (GCP) perspective.

Dissecting the Form FDA 1572 for Principal Investigators and Sub-Investigators

Sections 1 and 2

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION **STATEMENT OF INVESTIGATOR** ***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*** (See instructions on reverse side.)	Form Approved: OMB No. 0910-0014 Expiration Date: March 31, 2022 *See OMB Statement on Reverse.* **NOTE:** No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR			
Name of Clinical Investigator			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select **one** of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

Important notes to keep in mind when filling Sections 1 and 2 include:

- Section 1: The name of the PI must match his/her legal name as it appears on legal documents, certificates, or qualifications (e.g., birth certificates, marriage certificate, medical licenses, or other titles). In cases when a co-investigator is assigned, then under 21 CFR 312.3 (b) the co-investigator must fill out and sign a separate 1572 form.
- The address to provide in Section 1 of the 1572 is for the PI's office, study site, or other business place where he/she can be reached by mail or in person.
- In any case when the PI is replaced with another investigator, Section 1 must be updated by filling out a new 1572 and supporting all required documentation listed in Section 2 in this form.{2}
- Section 2: Requires attachment of all investigators' *curricula vitae* (CVs) or "Other Statement of Qualifications" showing the education, training, and experience that qualifies the investigator as an expert in the conduct of the clinical trial of the drug/biologic under investigation.

Frequently Asked Questions for Sections 1 and 2

Q: What qualifications are needed to be assigned as a PI?

A: There are no specific requirements stated by the FDA in terms of the PI's qualifications. However, sponsors will always aim to select PIs who are qualified by training and experience to conduct the clinical trial, including their familiarity with human subject protection regulations (i.e., 21 CFR Parts 50 and 56) and GCP regulations (see 21 CFR Part 312).{2}

Q: Is it necessary that the assigned PI be a physician?

A: Again, the sponsor selects PIs who are qualified by training and experience to conduct the clinical trial, but there are no minimum requirements for the PI to be a physician. In cases when the sponsor selects a PI who is not a physician, a qualified sub- investigator (physician) must be listed on the 1572 for the trial to make all medical-related decisions.{4}

Sections 4 and 5

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY			CONTINUATION PAGE for Item 4
Name of Clinical Laboratory Facility			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code
5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)			CONTINUATION PAGE for Item 5
Name of IRB			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

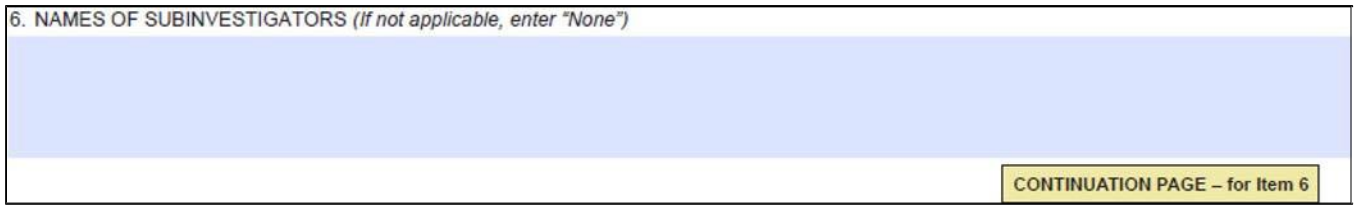
Frequently Asked Questions for Sections 4 and 5

Q: What types of laboratories should be listed in this section?

A: Note that it is vital to list all clinical laboratories or clinics that primarily conduct tests that are required or part of the clinical study. The listing of laboratories is not limited to laboratories conducting blood work, X-rays, etc.; it is very important to include any laboratories supporting pharmacokinetic and efficacy analyses for clinical trials listed under an IND application. In cases when the clinical laboratories or facilities are using another contract lab or satellite location, it is required that only the primary laboratory be listed, where it is used as a point of reference to trace samples to each of the contracted labs or satellites.{5}

Further, you should list all involved IRBs that will be reviewing and approving all related study materials.{2}

Section 6

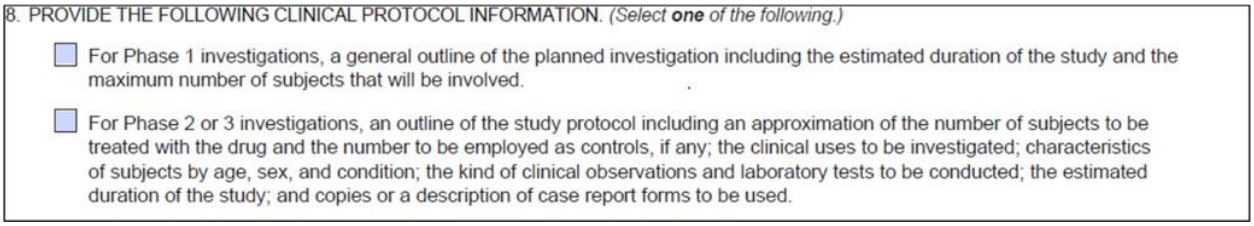


Section 6 is provided for delivering names of individuals listed as sub-investigators. According to 21 CFR 312.3(b), when an investigational study is conducted by a team, the PI is the sole lead of this formed team. All individuals who are assisting the PI and directly contributing to conduct of study procedures specified in the protocol and generation of data must be listed as sub-investigators on the Form FDA 1572.

It is the responsibility of the PI to supervise the team and delegate responsibilities and tasks appropriately, based on the team members' qualifications, education, and training. Any other office staff who provide any type of care or service that does not contribute to the overall generation of the trials clinical data do not need to be listed as a sub-investigator.{4}

Use the Continuation Page if additional space is needed.

Section 8



- Check only one box that is applicable to the type of clinical trial being conducted.
- For combined Phase I and II clinical studies, check only one box.
- Check the second box for Phase IV clinical investigations.

Section 10

10. DATE *(mm/dd/yyyy)*	11. SIGNATURE OF INVESTIGATOR Sign

Important notes to keep in mind when filling Section 10 include the following:

- The date must represent the date the form was signed by the PI.
- The signature must match the individual's name listed in Section 1.
- Sites never directly submit this form to the FDA; once completed, it is necessary for the site to provide all the other documents requested along with this form in Section 2 to the sponsor.{5}

Common Mistakes Identified in Audits

- Submission of incorrectly completed forms.
- Missing submission of requested documents in Section 2, especially when study personnel have been added to the 1572 or in cases when the original PI has been replaced.
- Failure to submit updated 1572 forms to both IRBs and sponsors.
- Site not having CVs for all study personnel listed on the 1572 form.
- Site lacking copies of current medical license for the PI.
- Upon collecting CVs that are not specific templates, it very important to be mindful of data privacy issues and make sure no sensitive information is listed on study personnel CVs, such as Social Security numbers, family members' information, etc.
- CVs provided are not current within the last two years.
- Missing documentation within the PI's CV of the his/her affiliation with the site conducting the clinical trial.

Form FDA 1572 Expiration Date

The most recent version of the Form FDA 1572 can be obtained from www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf.

In cases when a Form FDA 1572 is being collected shortly before a new version is released, sponsors can use the current version to obtain signed agreements from clinical investigators participating in their clinical studies. The expiration date given for using the form reflects the U.S. Office of Management and Budget's clearance of the form as meeting the requirements of the Paperwork Reduction Act. Despite the fact the form carries an expiration date, there is no need to provide a new form after the new version with the latest expiration date has been released.

Conclusion

For new clinical research professionals entering the field or in need of a refresher to their current knowledge, this paper was written as a guide to all study site staff, including CRCs, CRAs, PIs, and sub-investigators. It is very important to understand the many regulatory documents used in clinical trials—what they mean and how to fill out and maintain them properly. As there may be many more details readers have questions about that are not covered in this article, please visit the references and resource cited below for any extra information needed.

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Resource

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Clinical Researcher—April 2019 (Volume 33, Issue 4)

CLIN OPS INSIGHTS

Why a Well-Planned Protocol Authoring Process is Critical for Successful Research

Priti Sahai, MBBS, MS

The clinical research protocol is the blueprint that determines a study's downstream activities, and it has an impact on all stages of the study—from design and planning to analysis and submission. The protocol describes the rationale for the research and how the study will be conducted. It provides important details such as background, objective, endpoints, schedule, statistical considerations, and other elements that offer clarity to all parties involved on what the study entails.

In other words, this critical document ensures that the investigators, study teams, institutional review board (IRB), and other administrative and regulatory bodies are all on the same page with respect to the study's concept, activities, and conduct. Therefore, getting the foundation right from the start and having a detailed and clearly written protocol provides a big boost toward ensuring that the study is completed on time, within budget, and in a safe and compliant manner.

Shedding Light on Protocol Development

Even though the importance of protocol authoring is widely acknowledged, many challenges that show up in clinical research projects can be traced back to issues with the protocol document. Common examples of such issues include lack of clarity, inconsistency, and missing information. These issues are generally addressable in the protocol authoring process, and would

not only prevent costly errors and delays, but also ensure a safe and effective process with fewer protocol violations. When such omissions or errors are discovered in the protocol, amendments are introduced leading to increased administrative burdens, expectations for retraining, and manual rework at levels which are detrimental to the overall study process.

A study conducted in 2010 by the Tufts Center for the Study of Drug Development examined protocol amendment data from more than 3,400 protocols from multiple phases and therapeutic areas. Nearly all protocols had at least one amendment, and more than a third of the amendments were categorized as being partially or completely avoidable. This excludes amendments that were made as a result of new safety information, regulatory requests, or changes in standard of care, but rather were due to flaws in the design and/or document.

Correlating this information with other data provided by the survey participants, it was observed that the direct cost resulting from a single protocol amendment was nearly $500,000, along with the addition of 61 days to the overall study duration. It is important to note that such unplanned expenses and delays come in addition to other challenges not as easily quantified (e.g., extra effort required by study teams, resubmissions, and other problems for the participating sites). Overall, the study estimated that in 2014 there was a cost of approximately $2 billion that could be attributed to avoidable protocol amendments for all active global U.S. Food and Drug Administration–regulated trials in that single year.

A Stitch in Time Saves Nine

The good news is that there are some simple yet concrete steps that can be taken to prevent such costly and time-consuming issues. Below are six points that can be incorporated easily into any research team's protocol authoring process to ensure a greater chance of success:

- *Begin with a structured approach*—When getting started, seek out content libraries, guidelines, and structured protocol templates that centralize and build upon knowledge bases available from prior studies and shared best practices. Templates and prior examples provide a helpful boilerplate for information that must be included in the protocol, ensuring that you don't miss key components. It's a good policy to begin with

the end in mind—the objective, the endpoints, etc.—and work your way through all the steps and processes needed to get you successfully to that point.

- *Save your homework*—During your explorations, it is important to keep records of references to all relevant background and supporting information, so that others reviewing and referring to the document are equally well informed about the research being undertaken. This also comes in handy when the researcher is looking at publishing an article.
- *Adopt a collaborative approach*—This has always been critical to research, but is even more important in current times, as research becomes increasingly complex and requires iterative review and input from an interdisciplinary team of experts. Collaboration is not just about the clinical, regulatory, safety, and statistical input that we seek, but also about insights from independent scientific reviewers, patient advocates, and peers, all of whom can provide important perspectives on matters not directly related to the specific research topic.
- *Document the authoring process, too*—Obviously, a key objective of this process is to have a final set of well-documented protocol material. However, remember that tracking the process and keeping a record of all key decisions made is extremely helpful—not just for future projects, but also should the need arise to review decisions or revisit issues in the current project.
- *Keep it simple*—Although it is important to keep detailed records of information gathered during the authoring phase, the protocol document should be kept as simple and devoid of inessential components as possible. The more complex the study's design and documents, the greater are the chances for misunderstandings, errors, and complications. Detailed information that isn't included in the protocol may be better served by being included in other material, such as the operations manual.
- *Ensure consistency*—While the above sections primarily address the protocol document, one should remain cognizant of other trial-related documents that require similar diligence and review (e.g., the consent form, the operations manual, and others). Sponsors and sites should work together to ensure consistency across the entire packet of documents being utilized in the study. Keeping this in mind at the authoring stage improves timelines for regulatory approvals and minimizes downstream issues.

Conclusion

Ultimately, it is a question of having a well-thought out plan early in the protocol authoring process and ensuring that a little more time and attention is spent upfront on key details. This decreases the likelihood of errors downstream due to omissions or misunderstandings, and increases the likelihood of success through a well-written, detailed, and clear blueprint for your research project.

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Clinical Researcher—April 2019 (Volume 33, Issue 4)

PI CORNER

Taking the First Steps on the Path to Being a PI

Elizabeth Weeks-Rowe, LVN, CCRA

There are fundamental steps a physician who is interested in conducting clinical research can take to best prepare for his or her new role as a principal investigator (PI). These tasks are integral to understanding such research tenets as patient safety, critical data, and investigator oversight. These activities will help a new investigator discriminate between clinical research and clinical practice, which can be a stumbling block in the overall assimilation to clinical research. Finally, these steps will demonstrate the investigator's due diligence in familiarizing with ALL responsibilities required for successful study conduct, and will give them a competitive edge (despite being new) when being evaluated for study participation.

To best prepare for the PI role:

1. Engage in complete, comprehensive Good Clinical Practice (GCP) training from a reputable industry vendor and/or a source recommended by an experienced research colleague. There are many credible online programs; however, this training should include more than basic human subjects protection by covering such topics as GCP, informed consent, institutional review boards (IRBs), investigator responsibilities, safety reporting/adverse events, investigational product handling, the Health Insurance Portability and Accountability Act, records/source document processes, and financial disclosure. This is not an all-inclusive list, but rather a guideline to ensure new investigator GCP training encompasses all required, impactful components of clinical trials.

2. Consider additional PI training; there are several online and/or classroom courses that include important, "behind-the-scenes" elements of the PI role, such as administrative and financial planning and strategizing for patient recruitment (i.e., other things critical to the PI role, outside the basic, participant-facing PI tasks).
3. Familiarize yourself with key portions of the *Code of Federal Regulations*: 21 CFR 50 (informed consent), 56 (IRBs), 11 (electronic records), 54 (financial disclosure), 312 (Investigational New Drugs), 314 (applications for U.S. Food and Drug Administration [FDA] approval to market a new drug).
4. Familiarize yourself with the International Council for Harmonization E6(R2) Guideline for GCP.
5. Familiarize yourself with the following FDA guidanances/information sheets (this is not an all-inclusive list—there are many insightful documents on the FDA website):

    - Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors
    - A Guide to Informed Consent
    - Exception from Informed Consent Requirements for Emergency Research
    - Recruiting Study Subjects
    - Using a Centralized IRB Review Process in Multicenter Clinical Trials
    - Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring
    - Use of Electronic Informed Consent: Questions and Answers

6. Review the FDA website for the contents of Warning Letters to familiarize yourself with what items are under specific scrutiny by the agency during an audit, and what are integral areas of compliance (https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm).
7. Align with an experienced PI for additional guidance, for such things as conduct of the first screening/baseline study visit for a subject, appropriate informed consent conduct/process, appropriate PI oversight, best training/communication practices for a research department, how to pick appropriate sub-investigators, etc. A strong mentor is imperative when learning to manage clinical trials, investigative staff, and patient safety.

8. Hire an experienced study nurse, study coordinator, or research administrator to facilitate the complicated regulatory and fiscal documentation associated with site activation and clinical trial conduct. Trying to expedite study start-up activities (contracts/IRB submissions are complicated enough for an experienced researcher) with a novice coordinator may set the investigator up for additional errors and submission delays. If both the PI and research coordinator/study nurse are new, it is critical to have an experienced research colleague or consultant to facilitate the activation process and meet the rapid and stringent timelines for study start-up chores.

During site selection:

1. During a pre-study/site evaluation visit, transparency is key regarding research experience. The investigator should disclose his/her new investigator status on feasibility questionnaires and to the clinical research associate (CRA) assessing the site. This honesty creates a platform from which investigators can stand out and strengthen their status by:
    - capitalizing on all efforts to prepare for their role and thus study success;
    - producing all documentation of training completed during their familiarization;
    - informing the CRA of alliances with other experienced investigators to further understanding of investigator tasks/responsibilities; and
    - hiring experienced study staff to support the activation and overall assimilation process.
2. Ensure the investigator's CV reflects any study experience (in preclinical settings, as a sub-investigator, etc.), therapeutic expertise, and all study training completed.
3. Demonstrate access to the study population with redacted database reports of potential study patients. This can be done via a specific search from a practice database or a clinical trials management system.

These steps do MATTER, and following them will help mitigate any unease felt (by the sponsor) regarding a PI's inexperience. A key factor to remember is that diligence, follow-through, integrity, and enthusiasm are strong investigator traits, and are not limited to those with research experience.

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Clinical Researcher—April 2019 (Volume 33, Issue 4)

SPECIAL ADVERTISING SUPPLEMENT

The Burden of Research on Physician Practices: Is Relief in Sight?

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Engaging in clinical research offers many advantages to private physicians. Providing the best possible patient care with the widest possible selection of up-to-the-moment treatment options is the most obvious. Other benefits include adding a new revenue stream and attracting and retaining more patients with the promise of better, cutting-edge care. Lastly, playing a positive role in improving the standard of care can provide meaning and help combat burnout for a physician operating a modern medical practice with its heavy load of administrative duties.

It's no secret that for many physicians outside of academia, there are too many obstacles to conduct research — and there have been for a long time. As one participant aptly stated back in 2007 at a National Cancer Institute workshop on improving the quality of clinical trials, "There are virtually no incentives in this country for any doctor to enroll a patient in a clinical trial, and there are huge disincentives. Every [stakeholder in] the clinical trials program has to look at how they can eliminate the disincentives that they contribute to the process."[1]

Since then, increasing regulations, trial complexity, and competition for study patients have only made the need to eliminate barriers to trial participation more acute. Read on as we outline four major burdens — and ways they can be relieved.

Managing Research — as a Business

Physicians often underestimate the intricacies of administering a clinical research program. To function as a successful, profitable business, a practice must establish the proper infrastructure. This foundation includes operations, financial resources, strategic staffing and training, technology, and attention to regulations.

As with any business, managing cash flow is crucial. Payments, collections, salaries, and budget negotiations must all be handled correctly to ensure good ROI. Hiring, training, and other HR functions must be performed. Furthermore, clinical research entails burdensome regulatory reporting requirements and complex data entry processes and systems.

These managerial tasks demand much more time and energy than most principal investigators (PIs) can afford. Fortunately, site management services can provide physician practices with

infrastructure or even training and assistance in these areas, including recruiting, staffing, technological solutions, evaluation of accounting records to assess uncollected revenue, and more.

Finding the Next Study

Often, non-academic investigative sites fail because they don't have a steady pipeline of new studies. Searching for the next project can be another burden that a busy practice can't afford, and repeated failures to find appropriate trials can siphon away enthusiasm for doing research.

However, PIs associated with site networks generally have access to a steadier stream of studies. Site management business development teams seek out new opportunities to share with partner investigators, who then may decide whether studies presented are appropriate for their practices. A steady pipeline means a more consistent backlog of studies for a research team, helping to keep the clinical trial business thriving.

Slow Study Startup

Study startup is notoriously inefficient. During investigative site identification, selection, and activation, investigators often repeatedly submit the same documentation, such as copies of medical licenses, training records, CVs, and confidentiality agreements. Study-specific filing and record-keeping take up yet more time.

Investigators can benefit from assistance to streamline procedures and avoid startup delays. Frenova, for instance, has demonstrated the ability to start studies in half the time of industry averages. This improvement entails the use of master clinical trial documents and a regulatory document database. Sites with these tools in place ahead of time find negotiating less complex and can execute new agreements rapidly.

Centralized study administration can provide the business and operational expertise not only to eliminate repetitive steps, but also to coordinate necessary activities, such as site identification, patient follow-up for improved protocol adherence, ethical reviews, and regulatory submissions.

In a 2009 survey, 49 percent of startup delays were attributable to prolonged contract negotiations[2] and are likely responsible for most of the site activation attempts that fail. Furthermore, ineffectual contract negotiations also cost investigator sites thousands of dollars in underestimated expenses. Engagement of site management services with personnel experienced in negotiating contracts on sites' behalf can accelerate study startup and ensure sites are compensated appropriately.

Locating and Enrolling Patients

Perhaps the most difficult part of conducting studies is enrolling patients. Patient enrollment typically accounts for 35 – 50 percent of a trial's timeline. Only 52 percent of clinical research sites reach enrollment targets, while 11 percent enroll no patients at all. Compounding this problem are increasingly complex study protocols with narrow eligibility requirements.

Finding eligible patients, informing them of the clinical trial, educating them about the importance of clinical research, and, finally, enrolling them require many hours of work. A busy physician practice rarely has the human resources with the requisite time or skills to accomplish these tasks. Extra staff must be brought on board but hiring them and managing them also requires time.

Investigative sites can get site management help for some of these functions. Patient counseling, follow-up, informed consent and other paperwork may be performed by externally managed site coordinators. Partnering with a site management company may mean access to other resources that can help speed enrollment and reduce the time spent on patient recruitment. Patient databases, area physician outreach, and community outreach such as advertising, web initiatives, or call centers may assist in locating patients.

A site management company may also engage in protocol feasibility assessments to optimize study designs, making the requirements practicable in the investigational setting and more palatable to patients and caregivers, thus easing recruitment and retention. An added benefit is robust protocols that do not require amendment, a great benefit as Phase III protocol amendments cost — on average — $535,000 and expend two-three extra months.[4]

Conclusion

For physicians, clinical research provides important benefits including the ability to offer patients more options, additional revenue, and job satisfaction. However, most physician practices are ill-equipped to handle the burdens that accompany study conduct and they abandon the idea: In a 2017 survey of 201 PIs, more than half quit after their first trial.[5]

The burdens include managing unexpectedly complex business and reporting responsibilities, finding trials to conduct, negotiating cumbersome study startup requirements, and finding and enrolling patients. All these functions entail more time, expense, and expertise than most PIs anticipate and easily overtax a busy medical practice.

Fortunately, site management companies offer expert guidance and support for management, streamlined startup, human resources and training, technology upgrades, contract negotiation expertise, and day-to-day, on-site study administration. Obtaining outside support is an efficient clinical research site strategy that allows investigators to concentrate on patient care and recruitment, mitigates challenges, and maximizes site performance and success.

About Frenova Renal Research

Frenova is the only Phase I-IV drug and device clinical development services provider dedicated exclusively to renal research. Backed by Fresenius Medical Care North America (FMCNA), the world's largest provider of dialysis services with a network of 2,400 dialysis clinics, 250 research sites and more than 450 principal investigators, Frenova is an unparalleled resource for biotech, pharmaceutical and medical device companies worldwide.
Visit www.FrenovaRenalResearch.com for more information.

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