

# Clinical Researcher™

**The Authority In Ethical, Responsible Clinical Research**

**September 2020 (Volume 34, Issue 8)**



**Good Study Streamlining Practices: Speeding (Safely) for the Finish Line**

## **Clinical Researcher™**

### **Association of Clinical Research Professionals**

#### **Editor-in-Chief**

**James Michael Causey**  
[mcausey@acrpnet.org](mailto:mcausey@acrpnet.org)  
(703) 253-6274

#### **Managing Editor**

**Gary W. Cramer**  
[gcramer@acrpnet.org](mailto:gcramer@acrpnet.org)  
(703) 258-3504

#### **Director, Advertising & Exhibition Sales**

**Tammy B. Myers, CEM**  
[tammy.myers@acrpnet.org](mailto:tammy.myers@acrpnet.org)  
(703) 254-8112

#### **Media Kit**

<https://acrpnet.org/advertising/>

For membership questions, contact ACRP at [support@acrpnet.org](mailto:support@acrpnet.org) or (703) 254-8100.

### **Editorial Advisors for This Issue**

**Victor Chen, MSc (The CK Clinical Group/Align Technology, Inc.)**

**Staci Horvath, CCRA (Gradalis, Inc.)**

**Stefanie La Manna, PhD, MPH, ARNP, FNP-C (Nova Southeastern University)**

**Christina L. Nance, PhD, CPI, FAACAI (Baylor College of Medicine/Texas Children's Hospital)**

## Table of Contents

**4 Executive Director’s Message—Some Self-Reflection for the Clinical Researcher Soul**  
Jim Kremidas

## PEER REVIEWED

**5 Clinical Study Reports 101: Tips and Tricks for the Novice**  
Sheryl Stewart, MCR, CCRP

**16 Opinion: The Significance of Clinical Trial Transparency During the COVID-19 Pandemic**  
Dr. Kumari Priyanka, BDS, PGDCR; Tejas Thomas, MSc, PGDCR

## SPECIAL FEATURES

**29 Risk-Based Monitoring of Clinical Trials: COVID-19 and Paving the Road to the Future**  
Sandra “SAM” Sather, MS, BSN, CCRC, CCRA, FACRP; Jennifer Lawyer, RN, BS

**38 The COVID-19 Effect: How to Maintain the Speed-to-Market Medical Model**  
Astha Bhatia, BDS, MPH

## COLUMNS

**44 Recruitment & Retention—RACE for Children Act Aims to Improve Pediatric Cancer Care**  
Lynne Georgopoulos, RN, MSHS, RAC; S. Y. Amy Cheung, PhD

**49 Science & Society—Innovations are Expanding the Possibilities for Addressing COVID-19**  
Al O. Pacino; Yonnie Otieno

**53 Site Strategies—Transparency is the Right Tactic With Your Site Staff, Too**  
Elizabeth Weeks-Rowe, LVN, CCRA

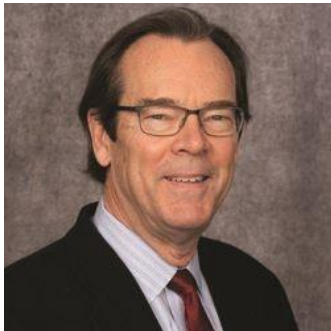


For information on writing a column or submitting an article for peer review for an upcoming issue of *Clinical Researcher*, visit <https://www.acrpnet.org/resources/clinical-researcher/> or e-mail [gcramer@acrpn.net](mailto:gcramer@acrpn.net). There will be no October 2020 issue. Nine issues will be produced in 2021, with February, June, and October being skipped. Credit-granting Home Study tests based on *Clinical Researcher* articles are available for purchase at <https://www.acrpnet.org/home-study/>, along with downloadable PDFs of the relevant articles and questions from each issue. The test based on this issue should be activated online in October 2020.

EXECUTIVE DIRECTOR'S MESSAGE

## Some Self-Reflection for the Clinical Researcher Soul

Jim Kremidas



We recently published a letter in the *Washington Post* [calling for greater diversity](#) in both the clinical trial patient population and workforce. The response has been heartening and overwhelming. I've heard from hundreds of people—members and non-members of ACRP alike—thanking us for speaking out, asking us how they can help, and otherwise supporting our shared goals.

We've also produced a number of insightful interviews with industry professionals talking about their experiences promoting diversity in the trial workforce and patient population for [ACRPTV](#). Like our recent item in the *Post*, these segments are sparking good conversation and, hopefully, helping us take steps toward identifying and harnessing new solutions.

I don't need to tell you these are simultaneously challenging and exciting times for the clinical research enterprise. We're faced with a global pandemic that's stretching our capabilities to the limit—yet clinical trial professionals are rising to the occasion with skill and dedication.

These are also exciting times because the COVID-19 catalyst has forced us to rethink how we conduct trials. It's made us take a closer look at our rationales, the tools we leverage (and don't), and even our own mindsets professionally and personally.

We have been handed a rare opportunity as an industry to retain our best aspects and fuse them with new approaches—whether it is promoting clinical trial diversity in the workforce and patient population, embracing new technologies, leveraging new concepts such as decentralized clinical trials, or taking advantage of other exciting innovations to the benefit of our participants.

I'm excited about the future, and I hope you are too. Thank you for everything you do. As always, I'd love to hear from you with your ideas and concerns about our enterprise.

**Jim Kremidas** ([jkremidas@acrpn.net](mailto:jkremidas@acrpn.net)) is Executive Director of ACRP.

PEER REVIEWED

## **Clinical Study Reports 101: Tips and Tricks for the Novice**

Sheryl Stewart, MCR, CCRP



*The tenets of Good Clinical Practice (GCP), promulgated by the International Council for Harmonization (ICH), require that investigator-initiated trials (IITs), especially those involving an Investigational New Drug application to the U.S. Food and Drug Administration (FDA), have the principal investigator (PI), the institution, and the study team assume roles of both the sponsor (ICH GCP E6(R2), Section 5) and of the PI (ICH GCP E6(R2), Section 4).{1} If you are part*

*of an IIT team, whether you are the investigator, a clinical research coordinator, or someone working in any of the many other important roles within the team, you may be tasked with authoring a clinical study report (CSR) at one time or another within the course of the study. At the very least, you may be asked to contribute to, or provide peer review of the document before it is submitted for its intended purpose.*

*The purpose of this review is to provide a framework for study team members, whether it's for a large team that includes regulatory and administrative support or for smaller teams with only one or two members, for writing and organizing the CSR.*

## Background

First, it is important to understand the definition, requirements, and potential uses of a CSR. The report is a comprehensive look at all the data produced in a clinical study, presented in text, tables, and figure formats. It will often include discussions and conclusions that provide context to the findings regarding the drug, device, biological product, surgical method, counseling practice, or any other type of therapeutic product or practice under study and where it may contribute to an improvement on the state of the art for treating or preventing a particular health condition.

If a study has prespecified endpoints or parameters, the CSR will report the current outcomes and statistical parameters for these endpoints. Key messages will be referred to and highlighted throughout. Key messages are important study findings that support the prespecified endpoints, supply proof of the justification of clinical benefit, or differentiate the study product from others in the therapeutic space.

Most likely you already appreciate the ethical responsibility a clinical study team has to clinical study data transparency, which for that reason alone would make the production of some sort of CSR necessary. Indeed, the preparation and representation of study progress is prescribed in the aforementioned ICH GCP E6(R2) guideline,<sup>{1}</sup> which states that study sponsors should ensure that clinical trial reports are prepared and provided to regulatory agencies as they are required.

Further, the guideline recommends study sponsors to rely on a subsequent guideline on Structure and Content of Clinical Study Reports (ICH E3).<sup>{2}</sup> Lastly, adhering to this ethical responsibility and following GCP have become mandated both in the U.S. and in Europe, where study data are expected to be recorded on ClinicalTrials.gov and the EudraCT database, respectively, for the sake of transparency and in support of further scientific inquiry, thus making the organization and preparation of study data in a prespecified format necessary.<sup>{3,4}</sup>

There are a few different uses for a CSR, though primarily it is utilized either to summarize the data and outcomes at the end of the study, or for marketing authorization. Those two purposes

are specifically outlined in ICH E3 and ICH E6.{1,2} However, a CSR may also be written for third-party payer reimbursement purposes, providing details in support of clinical benefit. Because in most cases CSRs will ultimately have a regulatory reviewer, authoring a report that is consistent in formatting and content with what is expected will hopefully not only enable a smooth review, but also will facilitate proper data cleaning, presentation, and timeliness that make the document fit for purpose.

## **Templates**

ICH E3 offers a CSR template to guide you in terms of providing the proper data and content in a specified order and format. This guideline can be found either on the ICH website or the FDA website.{2,5}

It is important to note that there are no requirements to follow the template precisely. Not every section is appropriate for every study, and because the overarching purpose of a CSR is to provide proper representation of the study data and any key messages you want to report, flexibility is allowed and encouraged in order to meet those important goals. However, for anyone new to the process of crafting a CSR, this template is a helpful starting point.

Transcelerate Biopharma, a nonprofit organization involved in researching means to increase efficiency and innovation in the pharmaceutical research sciences, also has interpreted the ICH template and has produced a useful tool to improve this reporting.{6} If the instruction and guidance in the ICH or Transcelerate templates do not meet your needs, or you have further questions as to how to properly represent the study data, the CORE reference manual (Clarity and Openness in Reporting E3-based) is another resource. It was produced in 2016 in response to regulatory changes for public disclosure of clinical study data, and can provide direction and interpretation of the ICH E3 template.{7}

For the novice author of a CSR, however, the ICH E3 template, coupled with the Transcelerate template, should provide a strong starting point for the project planning of the report, as well as the document formatting.

## Sidebar: Tips and Tricks for Getting Started

- **Review the template sections and start collecting the necessary documents you'll need to review and refer to in the document, such as the protocol, investigator brochure, monitoring plan, and the statistical analysis plan.**
- **Create a Microsoft™ (MS) Word document using template headings and list levels to help organize your thoughts about the project, draft the initial outline of the document, and to plan next steps in collecting information.**
  - **If MS Word is not a strong skillset for you, consider taking a MS Word course. There are many helpful online courses to assist with formatting, captions, redlining, pagination, headers/footers, etc.**
- **Save document with an additional backup on the computer and in a cloud-based, secure file with limited access.**

## Determining Stakeholders

Once you've reviewed the template and created a draft outline of the project, determine the key stakeholders with whom you'll need to partner to complete this project. Likely you will need input from your clinical study management team, teammates responsible for data entering and cleaning, a biostatistician, any teammate or organization member able to perform literature reviews, those staff qualified to compose patient or adverse event narratives, and those team members who can help determine key messaging in this report. Lastly you will want to determine the group of key stakeholders who will be your final review team for the document—those who will help you finalize the document prior to submission.

## Sidebar: Tips and Tricks for Stakeholder and Project Management

- **Identify the stakeholders for each section of the template per section (statistician, data management team, content experts).**
- **Collect and review resources, including any previous study publications, presentations, or reporting for any key messaging about the study drug, similar drugs, or the disease under study.**
- **Consider drafting a project charter or scope document to ensure commitment from all required teammates on scope, deliverables, and timelines.**



## Determining Timelines

Once you have determined your key stakeholders, you will want to determine timelines to ensure steady progress continues to be made on the document. If you've chosen to utilize a scope document, you'll want to include these timelines in it, so the entire team is aware of the project process, the timing requirements, and each gating item (key gating items are summarized in Figure 1).

**Figure 1: Preparing, Writing, and Review of the Clinical Study Report—Key Gating Items**

Preparation of Data	Writing and Document Review
<ul style="list-style-type: none"><li>○ Data cleaning and query resolution</li></ul>	<ul style="list-style-type: none"><li>○ Write non-results sections</li></ul>
<ul style="list-style-type: none"><li>○ Plan tables, listings, and figures (TLFs)</li></ul>	<ul style="list-style-type: none"><li>○ Perform literature review</li></ul>
<ul style="list-style-type: none"><li>○ TLF creation and revisions</li></ul>	<ul style="list-style-type: none"><li>○ Write results sections</li></ul>
<ul style="list-style-type: none"><li>○ TLF editing</li></ul>	<ul style="list-style-type: none"><li>○ Cross team/stakeholder review</li></ul>
<ul style="list-style-type: none"><li>○ Data-lock process</li></ul>	<ul style="list-style-type: none"><li>○ Incorporation of revisions</li></ul>
<ul style="list-style-type: none"><li>○ Final TLF preparation</li></ul>	<ul style="list-style-type: none"><li>○ Finalize report for submission</li></ul>

Time management is paramount for clinical trial submissions to regulatory authorities. Attendees at medical writing conferences over the course of a five-year period (2008 to 2013, n=78) were surveyed to determine to how long each step of the CSR process can typically require. {8}

To complete a “moderately complex” CSR for a Phase III study with 200 to 400 participants, the surveyed medical writers responded with a mean answer of 16.9 days from the receipt of the final tables, listings, and figures (TLFs) to delivery of the first draft of the CSR. They estimated a mean of 25.7 days from the first draft to the final draft routed for review. The time from database lock to completion was reported to be on average 83 days.

While there was a wide range for the timelines reported, these data provide the novice CSR author a basic reference point for how long the individual processes can expect to take with

experienced medical writers. Fortunately, while TLFs are being crafted, multiple other “Writing and Document Review” tasks from Table 1 can be performed simultaneously.

### **At Last...the Writing!**

Typically, the flow of your CSR will progress under six primary headings or sections, not unlike those used in a research manuscript. On the front end, even before the background and introduction, the document will include a title page, synopsis, table of contents, list of abbreviations, ethics statements, and details on the study’s administrative structure. The primary sections to come after that are highlighted in Figure 2 and summarized in turn below.

**Figure 2: Primary Sections**



#### *Background and Introduction*

When available, utilize any state-of-the-art analysis of the product/therapy from the protocol for your CSR introduction. If not available, you can briefly summarize the study design, objectives, and population and then you’ll need to craft a novel but brief state-of-the-art analysis based on literature review.

Be sure to align with the key messaging of your study and the indications of your study drug, device, or other type of therapeutic product or method. Utilize good literature review practices, such as choosing peer-reviewed publications, editorials from key opinion leaders in the therapeutic area, and studies with large or randomized cohorts, for support. This section will likely be no longer than one page.

### *Non-Results Section*

Whether to cut and paste the procedures and assessments, primary and secondary endpoints, parameters or hypotheses, planned statistical analyses, monitoring plans, adverse event definitions, and assessment rules directly from the protocol or to simply refer to the protocol and the other study documents in an appendix is a topic of debate amongst medical writers of CSRs. Keep in mind that the CSR should be able to stand alone as a document, and thus while it is important to keep the document concise, it must be comprehensive enough for the reader to understand the study design, objectives, endpoints, processes, and intended analyses without having to refer constantly to the protocol. Regardless, in any summary of the study design, processes, and endpoints, be sure to align with any previously utilized language for consistency across study documents.

### *Results Section*

Using the template and your tables as your structure, summarize the data and pull out any signals and trends, aligning with key messaging where possible. Start with patient disposition and demographics as per the template. Note any protocol deviations that may or may not have impacted patient safety or the evaluation of the outcomes.

Assess and evaluate the study outcome results against primary endpoints and secondary endpoints before discussing any additional secondary outcomes. You should not simply restate the data in the tables; however, refer to specifics in the tables when summarizing.

If you find that you cannot make a statement or conclusion given the TLFs you have, or you are consistently having to perform your own math to support your statements, consider asking your biostatistician to create the tables that will represent the data in a way that will better support your statement. For instance, it is acceptable to state that “most” of the patients responded to the study drug if more than 50% did so; however, if you are having to consistently add up percentages in a table to be able to state, for example, that 77% of the patients responded in a certain way and 33% responded in another, then you should have the biostatistician reformat the data output so it represents the percentages you want to report.

Patient narratives are an important source of context for the reader of the CSR. Depending on your study, you may need to collaborate with either your teammates responsible for assessment of adverse events or the study database administrator to help generate patient and/or event narratives for the CSR. If tasked with compiling or editing patient narratives yourself, the ICH E3 guideline prescribes the necessary components of a comprehensive patient safety narrative (Section 12).{2}

Narrative writing advice has also been previously published and would be a helpful source of direction for the novice narrative writer.{9,10} Narratives are suggested for every patient who experienced a safety endpoint event or death during the course of the study. Tie in patient narratives where appropriate when discussing safety events or refer to the patient narrative section when highlighting a particular patient’s data.

### *Discussions and Conclusions*

Discussion and conclusion sections can either be placed after each section or placed at the end of the document. They should not simply restate the previous table summaries, but provide context and align the results with key messaging. Use an evidence-based approach, including literature references to provide more context as to the nature of the study outcomes with respect to the state of the art for the product/therapy, outcomes from alternate approaches, or further justification of clinical benefit with regard to potential disease progression. The conclusion section at the end of the document is often in bulleted format—not only for ease of the reader, but also to clearly highlight the key messaging and important outcomes you wish to impart.

### *Executive Summary*

The executive summary, while placed at the front of the document prior to the introduction, is often easiest to construct last, as an overall summary of the entire document. The key elements of this summary should briefly recap the study design and objectives. Most likely only the primary and secondary endpoints should be included, unless additional outcomes proved compelling and important within the course of the study. Refer to any important literature comparisons as they

relate to any conclusions made about the success or outcomes of the trials. Conclude the executive summary in a similar fashion to the overall study conclusion.

### **Sidebar: Tips and Tricks for the CSR Writing Process**

- **Create all headings and/or multilevel lists before you start writing.**
- **Request a “soft” database extract and a pre-run of the TLFs.**
  - **Often this first quick look at the TLFs will reveal any discrepancies in data entry or queries that can then be resolved before the TLFs undergo the larger review process.**
- **Begin a rough draft of the results sections from these early tables. Though some changes in the data will likely occur, most data will stay the same and key messages will remain valid, thus you can get a head start on the document while waiting for final tables.**
- **Insert TLFs without captions until you are sure you will not be updating or switching out tables.**
- **Wait until the end of the review process to:**
  - **Create any hyperlinks**
  - **Finalize your table of contents and table of figures**
  - **Insert your bibliography**
  - **Insert your listings and appendices**

### **Review Process**

The review process can either facilitate a better document or it can slow down the entire process. The purpose of a cross functional review of a CSR is to confirm accurate key study messaging and data; allow medical review of the patient narratives, outcomes, and conclusionary statements; review the logical flow of ideas; and ensure that the CSR language is consistent across any other study document (i.e., the protocol, statistical analysis plan, etc.).

## Sidebar: Tips and Tricks for an Efficient Review Process

- **Request reviewers to initially review for content, as errors in formatting, grammar, and spelling are fine to notate, but are much less important (and likely will be caught later) than providing content review.**
- **Start the review team working on the non-results section first and finalize it before sending them the results section.**
- **Discourage the review team from backtracking to the non-results section, as it should be considered finalized unless something major changes.**
- **Maintain the documents for review in a secured, shared, cloud-based content management application, such as Box.com, so reviewers can review and provide revisions in real time with each other and avoid version confusion.**

## Conclusion

CSRs are required by regulatory authorities to report and summarize the outcomes of a clinical study. Pre-project stakeholder determination and timeline planning can help with project management. Templates contained with the ICH E3 guideline can help organize the project as well as help create and finalize a document that is fit for purpose and meets the content expectations of the regulatory reviewer.

## References

1. ICH Working Group. 2016. *ICH HARMONISED GUIDELINE INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2)*.
2. ICH Working Group. 1995. *ICH HARMONISED TRIPARTITE GUIDELINE: Structure and Content of Clinical Study Reports E3*.
3. U.S. Department of Health and Human Services. 2016. *Clinical Trials Registration and Results Information Submission, 42 CFR Part 11*.  
<https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>
4. European Commission. 2001. *Letter to Stakeholders Regarding the Requirements to provide results for Authortied clinical trials in EUDRACT. In: Article 57(2) Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006*.  
<https://eudract.ema.europa.eu/>

5. U.S. Food and Drug Administration. 2018. *ICH Guidance Documents*. <https://www.fda.gov/science-research/guidance-documents-including-information-sheets-and-notices/ich-guidance-documents>
6. Transcelerate Biopharma Inc. Clinical Template Suite (CTS), Template, Resources, and Use Guidance. <https://transceleratebiopharmainc.com/assets/clinical-content-reuse-assets/>
7. Hamilton S, Bernstein AB, Blakey G, et al. 2016. Developing the Clarity and Openness in Reporting: E3-based (CORE) Reference user manual for creation of clinical study reports in the era of clinical trial transparency. *Research integrity and peer review*. 1:4.
8. Hamilton S. 2014. Effective authoring of clinical study reports. *Medical Writing* 23(2).
9. Nambiar I. 2018. Analysis of serious adverse event: Writing a narrative. *Perspect Clin Res* 9(2):103–6.
10. Ledade SD, Jain SN, Darji AA, Gupta VH. 2017. Narrative writing: Effective ways and best practices. *Perspect Clin Res* 8(2):58–62.



**Sheryl Stewart, MCR, CCRP, ([ssstewart70@aol.com](mailto:ssstewart70@aol.com))** is a Medical Writer working in the medical device industry in southern California.

Clinical Researcher—September 2020 (Volume 34, Issue 8)

PEER REVIEWED

## **Opinion: The Significance of Clinical Trial Transparency During the COVID-19 Pandemic**

Dr. Kumari Priyanka, BDS, PGDCR; Tejas Thomas, MSc, PGDCR



*Clinical trials lay the foundation for biomedical research to generate robust evidence on the safety and effectiveness of proposed treatments and/or preventive interventions for eventual use in routine clinical care. Clinical trials directly engage volunteer participants who trust the investigators to conduct their studies based on the best available scientific knowledge and ethical practices.*

*In this paper, we consider how data sharing and transparency are important practices of research for the drug and device development industry to follow in order to maintain the trust and confidence of the public. We also relate the history of how these practices have been developed in the U.S. to their current importance in the midst of the COVID-19 pandemic.*



## **Background**

Issues surrounding clinical trial data transparency came to light with the first requirements for trial registration from the U.S. Food and Drug Administration (FDA) Modernization Act of 1997. This act mandated the establishment of a database for clinical trials of experimental drugs being used to treat life-threatening conditions.

In 2000, ClinicalTrials.gov went live to allow public access to clinical trial data. Over the last decade, several other milestones were implemented worldwide for maintaining clinical trial transparency and compliance.{1,2} The World Health Organization (WHO) and the Declaration of Helsinki have also stressed the importance of clinical trial transparency.{3,4}

Transparency in clinical trials begins with registering a trial on a public database and continues with access to patient-level data for subsequent analyses and publication of the trial results, irrespective of the outcome.{5} Several large pharmaceutical companies have initiated transparency methods to ensure their research practices are compliant with a variety of laws, regulations, and guidelines.{6,7} Many of them have also collaborated with external medical and scientific researchers to advance their clinical research and thereby enhance public health.

Despite widespread efforts by regulators and sponsors to ensure compliance and clinical data transparency for all clinical trials conducted globally, results and outcomes from only about half of all trials are ever published.{8} Overall, lack of transparency leads to serious implications for patients, healthcare professionals, and health systems.

## **The New Challenge**

On January 30, 2020, the WHO declared the novel acute respiratory infection caused by the SARS-CoV-2 virus, termed Coronavirus Disease-2019 (COVID-19), as a Public Health Emergency of International Concern.{9} As of July 20, 2020, more than 14 million people worldwide are confirmed to be infected, leading to increasing fatality rates.{10}

Numerous pharmaceutical companies and research institutions are conducting clinical trials to develop new or repurposed medicines and other therapies to combat COVID-19. More articles

are published each day on potential treatments or diagnostics for this pandemic, but evidence on the efficacy and safety parameters of interventions seems to have been overpassed along the way. Thereby, regulatory authorities and medical professionals are facing difficulty in decision-making on the best treatment options.

In the past, regulators and sponsors have had differences of opinions in publishing their confidential and proprietary information and certain patient-level data. This may be the time to pause and re-analyze whether clinical trial transparency would help the world overcome this pandemic with the best treatment option available.

There are many controversies and diverse questions related to the importance of transparency that are yet to be answered. It is always debatable whether the industry is following the right track by disclosing or withholding certain clinical trial data.

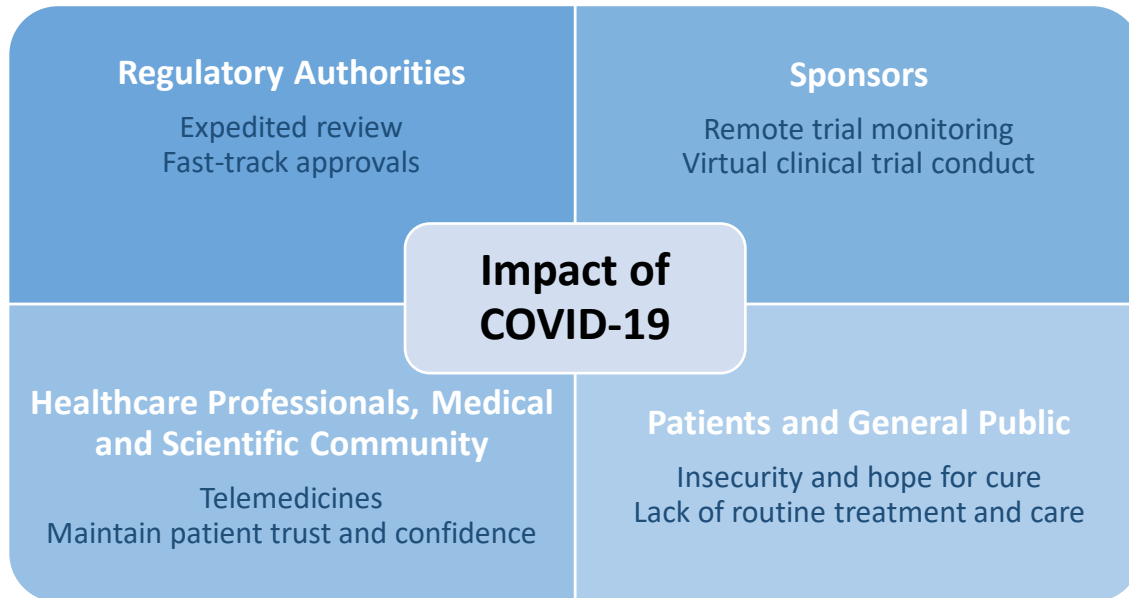
### **The Impact of COVID-19 on the Clinical Research Industry**

The outbreak of COVID-19 has created a global health crisis and has deeply impacted almost everyone's daily lives. Although COVID-19 has harmed the global economy, with many major businesses experiencing huge losses and countless small ones being forced to close, everyone is looking toward the clinical research industry as offering a ray of hope against a worst-case scenario for this outbreak.

Despite the many trials being conducted on COVID-19, due to a perceived lack of high-quality published trial data, some regulatory authorities and healthcare systems are expressing indecisiveness about the status quo of this worldwide effort. This could lead to a delay in availability of effective treatments, impacting public health and the global economy.

Across the industry, regulatory authorities, trial sponsors, healthcare professionals, and patients are facing serious challenges in fighting this pandemic (see Figure 1 for a summary). In the following sections of this paper, we will take a closer look at each of these sectors.

**Figure 1: Challenges Across Multiple Sectors from COVID-19**



### **Regulatory Authorities**

A number of regulatory authorities (the FDA, European Medicines Agency, Medicines and Healthcare products Regulatory Agency, Health Products Regulatory Authority, and others) have released several guidance documents and dedicated the work of various ethics committees to expediting regulatory and ethical review processes to maintain high standards during this pandemic.{11–15} Most of the regulators have also implemented a fast-track approval system considering human safety as priority.

For instance, the European Commission published Recommendation (European Union) 2020/403, considering the shortage of necessities during the outbreak to supply non-CE marked devices in the interest of protection of health, as long as they comply with necessary specifications. However, documentation is the key that would be required for any future inspection purposes.{16}

Some of the key initiatives from regulators deal with such concerns as those listed below {17–20}:

- Prioritize, expedite review, and provide fast-track approval for clinical trials devoted to COVID-19
- Engage ethics committees to ensure patient safety concerns
- Support sponsors to amend any existing trial protocols or suspend trials, if possible
- Encourage sponsors on matters related to remote trial monitoring and providing investigational medicinal products to trial participants
- Report serious adverse events and submit annual safety reports and end-of-trial notifications
- Provide waivers as necessary in case of protocol deviations and serious breaches

Regulatory bodies are working closely with innovators/sponsors to foster the development of safe and effective medical countermeasures against the COVID-19 pandemic. They are under extreme pressure to ensure that the best treatment options are available at the earliest to protect public health and safeguard the public from the use of fraudulent products claiming to prevent, treat, or diagnose COVID-19.

Despite several initiatives from regulatory authorities, many ongoing clinical trials are unregistered, and their data continue to be unavailable to both the general public and the scientific community. In addition, some trial data are not even being shared with regulators appropriately, leaving them handicapped in terms of enforcing standard drug approval processes and, in turn, in protecting the public.

### **Corporate Sponsors and Other Researchers**

Currently, there are no FDA-approved medical products for the prevention or treatment of COVID-19, and pharmaceutical company, academic, and government researchers are striving to find a potential drug candidate in record time. Globally, more than a hundred potential drug and vaccine candidates have been proposed to the WHO, but only a few are in the clinical evaluation stage. {21,22}

Certainly, technology and digital information could be the key to such rapid changes in the industry. Although there is room for flexibility, pragmatism, and speed, it is also important for sponsors and other researchers to adhere to well-established standards for quality, efficacy, and safety to promote the wellbeing of the public.

A whole new era of conducting virtual clinical trials is under way, and a great deal of responsibility rests on the shoulders of research teams to maintain patient safety and data integrity. Companies and institutions are evolving their capabilities and improving their methods for real-time data capture; moreover, many have deployed methods such as at-home care and remote monitoring to minimize the impact of pandemic conditions on ongoing clinical trials.{23–26}

FDA guidance issued in the context of COVID-19 also states that it is important to report any changes implemented during trials in the wake of the pandemic.{27} Henceforth, it is crucial for sponsors and other researchers to stay abreast of the concerns and guidelines of their local or regional regulatory agencies, and to document every action taken in their trials. Meanwhile, they should engage with sites, healthcare professionals, and patients to disclose study data appropriately.

### **Healthcare Professionals and the Medical and Scientific Community**

During this COVID-19 outbreak, healthcare professionals and research scientists are in urgent search of a remedy to provide quality treatment to their patients and improve their quality of life. At the same time, they must ensure that preventive medicine options are in place to protect the general public's safety.

There are several challenges that these professionals and the principal investigators of studies are currently encountering in terms of maintaining patients' trust while prioritizing safety:

- Out-of-home travel restrictions due to government-enforced lockdowns in several countries
- Steps being taken to implement telemedicine and telehealth systems
- The need for frequent communication with patients{28–30}

It is therefore important to maintain transparency at all stages of research, as this helps healthcare professionals to choose the right medicine and provide high-quality care and treatment to their patients.

### **Patients and the General Public**

The COVID-19 outbreak has left the general public clueless about many factors affecting its health and safety in pandemic conditions. Incomplete information about clinical trials and available treatment options are causing anxiety and confusion.

For example, many patients with chronic diseases who are trial subjects for non-COVID-19 conditions (and their caretakers) face dilemmas about their future care and treatment, as many ongoing clinical trials are being suspended or halted for safety concerns. {31,32} Patients may be required to self-isolate, causing more difficulties for trial investigators seeking to maintain medical oversight.

Meanwhile, we are seeing heightened urgency concerning who will have access and when to the results of COVID-19 trials as many companies and other research institutions race to cure this pandemic, which we will look at more closely in the next section. Any lack of clinical data transparency can cause patients to lose trust in their physicians and become extremely demotivated and insecure, leading to psychological and behavioral changes.

### **Importance of Clinical Trial Transparency During the COVID-19 Pandemic**

In the midst of these difficult pandemic conditions, research scientists and pharmaceutical companies are prompted to dive deep to find a solution to the novel viral infection and patients are demanding clinical trial information. Most regulatory guidelines allow 12 months to elapse between study completion and posting of the trial results to public registries. Although some regulations do not mandate clinical trial disclosure for early-phase trials, it would be worthwhile publishing important trial observations in the public domain sooner rather than later, especially in situations such as the pandemic. {33}

Currently, WHO data present several potential COVID-19 drugs and vaccines that are being tested in various ongoing clinical trials.{34,35} Several sponsors have claimed their potential drug or vaccine candidates to be in advanced stages of clinical trials, but have revealed only incomplete data and preliminary trial observations, leaving the community in a dilemma about the safety and efficacy of the medicine.{36–38} In the urgency of the situation, it is of utmost importance for sponsors to comply with regulations while also considering patient safety in disclosing essential critical trial data.

In light of the ongoing health crisis, let's consider the stakeholders and a few best practices each should follow that could benefit the clinical research industry and ultimately the whole world:

- **Regulatory authorities:** Availability and disclosure of full clinical trial data in a timely manner will help everyone to make the right decisions during the drug approval process. This will ensure that the best treatment option will be available as early as possible to overcome this global health crisis.
- **Corporate sponsors and other researchers:** Clinical data transparency could avoid duplication of research efforts and unnecessary financial losses while encouraging improvement in the design, conduct, and oversight of clinical trials, thereby providing appropriate diagnosis, treatment, and prevention of COVID-19.
- **Healthcare professionals and others in the medical community:** Appropriate disclosure of clinical trial data will help the medical community to make the right decisions in a timely manner by choosing the most effective therapies for the treatment and prevention of COVID-19. It could further help in explaining available experimental drugs or vaccines to COVID-19 patients. This will further enhance patients' confidence and trust in the entire healthcare system.
- **General public, including patients:** Access to real-time data for members of the general public will build confidence in existing healthcare systems and in the security of their own health. This could motivate more people to take more effective steps toward “flattening the curve” of this outbreak and others to come.

### **Guidance for Transparency: Trial Registration, Data Disclosure, and Reporting Practices**

As per the U.S. Final Rule (effective from January 18, 2017) for Clinical Trials Registration and Results Information Submission (42 CFR Part 11 in the *Code of Federal Regulations*) and Section 801 of the FDA Amendments Act (FDAAA 801) implemented in 2007, it is important for sponsors to register clinical trials on drugs, biological, and device products and submit their

results to the ClinicalTrials.gov registry.{39,40} Similarly, the Clinical Trial Regulation (EU) No 536/2014 in the European Union implemented a portal to register EU-based trials on a database to ensure transparency in their conduct.{41}

According to the WHO best practices, results from every clinical trial should be uploaded in the respective local trial registry no later than 12 months after primary or study completion date.{3} The regulations are enforced for the benefit of the sponsors, regulatory authorities, healthcare professionals, and patients. This could further enhance public confidence in the clinical trial process, new medicines, and regulatory systems. It could also help healthcare professionals in deciding on treatment options.

These measures are fostered to accelerate further research by accumulating knowledge and technical ability. Therefore, duplication of trials, safety or efficacy failures, redundant data, and workforce investment in research may be avoided, and this could stimulate growth and development of commercial and academic research centers, medical facilities, and research expertise.

Meanwhile, FDA guidance first released in March 2020 and revised in July 2020 provides insights to sponsors and investigators on maintaining compliance with the tenets of Good Clinical Practice and minimizing risks to trial integrity in these pandemic conditions.{20}

### **Navigating a New Regulatory Landscape**

The clinical research industry is adapting to rapid, pandemic-driven changes that have affected activities at all levels, starting from the regulatory authorities, sponsors, contract research organizations, and trial sites and reaching all the way to trial participants. There is more room for new technologies and start-up innovators to address the increasing demands of managing clinical trial data sources and remotely connecting with patients, to name just a few challenges.

Clinical trials are mostly patient-centered, and before long, the industry will be highly efficient in conducting clinical trials virtually with connected devices, medications delivered at home, and timely long-distance communication, therefore achieving accurate data capture and transparency and, at the same time, gaining and improving patient trust. Overall, the potential downside of



increasing dependence on technology would be that it cannot replace human interaction and deliver the physical care provided by doctors in person.

## **Conclusion**

COVID-19 is a severe and ongoing novel pandemic that has caused immense social and economic regression across the globe. Pharmaceutical companies worldwide are under public and competitive pressure to explore innovations in drug development and revamp their reputation.

During this time of increasing need for self-care and prevention, humankind is becoming even more dependent on technology and sponsors are implementing decentralized and stay-at-home clinical trials. Thereby, use of remote trial technologies could further overcome ethical and regulatory barriers to enhance patient safety and trial data integrity compared to traditional trial designs. However, lack of human connection in such conditions may have drawbacks that should be taken into consideration.

Pandemic situations definitely demand transparency in clinical trials. Lack of full, conclusive scientific evidence from the various ongoing COVID-19 trials could lead to ignorance of an effective treatment to curb the spread of the disease. Although there are various regulations and policies in place, sponsors and companies are still striving to understand the public scope of in-depth disclosure of trial plans and outcomes.

It is important for sponsor companies and others conducting studies to maintain high standards in research and to meet all regulatory and local requirements. Generally, bigger pharmaceutical companies are able to meet their compliance obligations with a dedicated team and all the requisite tools at hand, while smaller companies may fall short in disclosing data and/or meeting other expectations appropriately without significant external assistance. Nevertheless, smaller companies are gradually paving their way to gaining the necessary skills and resources.

Compliance also adds value to the credibility and reputation of these companies and researchers. Therefore, it is critical to report any observations and publish trial results appropriately to avoid any gaps in knowledge and deliver effective treatments for this global disaster. The future of

clinical trials could be overwhelmingly positive if we consolidate the advances being made now and proceed toward greater data transparency.

## References

1. Richardson E. 2016. Transparency in Clinical Research. <https://www.healthaffairs.org/doi/10.1377/hpb20160114.120263/full/>
2. History, Policies, and Laws. 2019. <https://clinicaltrials.gov/ct2/about-site/history>
3. World Health Organization. 2020. International Clinical Trials Registry Platform (ICTRP). <https://www.who.int/ictrp/results/jointstatement/en/index1.html>
4. Krleža-Jerić K, Lemmens T. 2009. 7th Revision of the Declaration of Helsinki: Good News for the Transparency of Clinical Trials. *Croatian Med J* 50:105–10. doi:10.3325/cmj.2009.50.105
5. About the Results Database. 2018. <https://clinicaltrials.gov/ct2/about-site/results#DisplayOfResults>
6. Novartis Position on Clinical Study Transparency – Clinical Study Registration, Results Reporting, and Data Sharing. 2016. <https://www.novartis.com/sites/www.novartis.com/files/clinical-trial-data-transparency.pdf>
7. Takeda Transparency Guideline. 2020. <https://www.takeda.com/who-we-are/company-information/Positions/folder/transparency-guideline/>
8. Mayor S. 2015. Most clinical trials fail to meet FDA requirement to publish results within a year. *BMJ* 350:h1333
9. Moorthy V, Henao Restrepo AM, Preziosi MP, Swaminathan S. 2020. Data sharing for novel coronavirus (COVID-19). *Bull World Health Organ* 98(3):150.
10. WHO Coronavirus Disease (COVID-19) Dashboard. 2020. <https://covid19.who.int>
11. Cox EM, Edmund AV, Kratz E, Lockwood SH, Shankar A. 2020. Regulatory Affairs 101: Introduction to Expedited Regulatory Pathways. *Clin Transl Sci* 13(3):451–61.
12. Clinical Trials Guidance Documents. 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents>
13. Background to clinical data publication policy. 2019. <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication/background-clinical-data-publication-policy>
14. Medicines & Healthcare products Regulatory Agency. 2020. <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency>
15. Health Products Regulatory Authority (Guidance Documents). 2020. <http://www.hpra.ie/homepage/about-us/publications-forms/guidance-documents#>
16. Pecchia L, Piaggio D, Maccaro A, Formisano C, Iadanza E. The Inadequacy of Regulatory Frameworks in Time of Crisis and in Low-Resource Settings: Personal Protective Equipment and COVID-19. 2020. *Health Technol (Berl)* 2020;1–9. doi:10.1007/s12553-020-00429-2

17. Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review. 2018. <https://www.fda.gov/patients/about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review>
18. Manley M, et al. COVID-19: regulatory implications for the UK and European life sciences industry. 2020. <https://www.europeanpharmaceuticalreview.com/article/116517/covid-19-regulatory-implications-for-the-uk-and-european-life-sciences-industry/>
19. Vignoli C. Regulatory Affairs – COVID-19: EMA Initiatives. 2020. <https://www.regulatorypharmanet.com/regulatory-affairs-covid-19-ema-initiatives/>
20. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency. 2020. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency>
21. Accelerating a safe and effective COVID-19 vaccine. 2020. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/accelerating-a-safe-and-effective-covid-19-vaccine>
22. Duddu P. Coronavirus treatment: Vaccines/drugs in the pipeline for COVID-19. 2020. <https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/>
23. Conducting Clinical Trials During the COVID-19 Public Health Emergency. 2020. <https://www.fda.gov/media/137496/download>
24. Will the Impact of COVID-19 on Clinical Trials Fast-Track Digital Health Technology? 2020. <https://www.mdmag.com/medical-news/impact-covid-19-trials-fast-track-digital-tech>
25. Remote Monitoring During Clinical Trials - COVID-19 Update. 2020. <https://www.quanticate.com/blog/bid/70489/remote-monitoring-during-clinical-trials-a-risk-based-approach>
26. Protecting Clinical Trials in Wake of COVID-19. 2020. <https://www.outsourcing-pharma.com/Headlines/Promotional-Features/Protecting-Clinical-Trials-in-Wake-of-COVID-19>
27. FDA Guidance on Conduct of Clinical Trials of Medical Products during. COVID-19 Public Health Emergency. 2020. <https://www.fda.gov/media/136238/download>
28. Chamola V, Hassija V, Gupta V, et al. 2020. A Comprehensive Review of the COVID-19 Pandemic and the Role of IoT, Drones, AI, Blockchain, and 5G in Managing Its Impact. *IEEE Access*. <https://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=9086010>
29. Siwicki B. 2020. Telemedicine during COVID-19: Benefits, limitations, burdens, adaptation. <https://www.healthcareitnews.com/news/telemedicine-during-covid-19-benefits-limitations-burdens-adaptation>
30. The impact of the Covid-19 pandemic on clinical trials. 2020. <https://www.clinicaltrialsarena.com/comment/covid-19-pandemic-clinical-trials/>
31. Coronavirus Pandemic Brings Hundreds of U.S. Clinical Trials to a Halt. 2020. <https://www.npr.org/sections/health-shots/2020/04/11/832210606/coronavirus-pandemic-brings-hundreds-of-u-s-clinical-trials-to-a-halt>
32. Ledford H. 2020. Coronavirus shuts down trials of drugs for multiple other diseases. <https://www.nature.com/articles/d41586-020-00889-6>

33. Clinical Trials Registration and Results Information Submission. 2016. <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>
34. World Health Organization. 2020. International Clinical Trials Registry Platform (ICTRP). <https://www.who.int/ictrp/results/en/>
35. COVID-19 Treatment and Vaccine Tracker. 2020. <https://covid-19tracker.milkeninstitute.org>
36. Draft landscape of COVID-19 candidate vaccines. 2020. <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>
37. Silverman E. 2020. Some Covid-19 trial sponsors never posted other study results in an EU database. Will they hide data again? <https://www.statnews.com/pharmalot/2020/06/17/covid19-coronavirus-clinical-trials-transparency/>
38. Bruckner T. 2020. Weak clinical trial reporting is undermining the search for effective COVID-19 treatments. [https://www-transparimed-org.cdn.ampproject.org/c/s/www.transparimed.org/single-post/2020/05/11/unreported-clinical-trials-Favipiravir-COVID-19?\\_amp](https://www-transparimed-org.cdn.ampproject.org/c/s/www.transparimed.org/single-post/2020/05/11/unreported-clinical-trials-Favipiravir-COVID-19?_amp)
39. Why Should I Register and Submit Results? 2011. <https://clinicaltrials.gov/ct2/manage-recs/background#WhyRegister>
40. FDAAA 801 and the Final Rule. 2019. <https://clinicaltrials.gov/ct2/manage-recs/fdaaa>
41. Clinical trials - Regulation EU No 536/2014. [https://ec.europa.eu/health/human-use/clinical-trials/regulation\\_en](https://ec.europa.eu/health/human-use/clinical-trials/regulation_en)



**Dr. Kumari Priyanka, BDS, PGDCR, ([kumari.priyanka@indegene.com](mailto:kumari.priyanka@indegene.com))** is Manager in Regulatory Solutions department at Indegene Pvt Ltd in Bangalore, India and lead author of this article. She leads Regulatory practice in Indegene with extensive experience in Regulatory Intelligence, Strategic Consultation, Regulatory Submission and Clinical Trial Disclosure services across geographies and product lines.



**Tejas Thomas, MSc, PGDCR, ([tejas.thomas@indegene.com](mailto:tejas.thomas@indegene.com))** is a Senior Regulatory Associate with Indegene Pvt Ltd, Bangalore, India. She is proficient in disclosure planning, tracking workflow related to trial transparency, and ensuring timely and accurate disclosure of clinical data as required by international law/guidance policy.

SPECIAL FEATURE

## **Risk-Based Monitoring of Clinical Trials: COVID-19 and Paving the Road to the Future**

Sandra "SAM" Sather, MS, BSN, CCRC, CCRA, FACRP; Jennifer Lawyer, RN, BS



Clinical research professionals are accustomed to sponsors requiring onsite monitoring to ensure human subject protection, data integrity, and quality. During the COVID-19 pandemic, however, clinical research sites have reduced the number of staff onsite and restricted onsite monitoring. Travel restrictions and the safety of the sponsor or contract research organization (CRO) monitors also compound the challenges of monitoring onsite.

Additional challenges have arisen with monitoring plans for active trials and trials that are soon to begin. These trials often support 100% source data verification (SDV), which is reviewing original data or certified copies to check for accuracy in the transcription into the electronic case report form (eCRF), and/or 100% data review of trial subjects, which is the monitoring of the quality of the data, the compliance to the protocol, and the completeness of reporting subject safety. This reveals a significant barrier to the ability to quickly shift to remote monitoring in the short term, due to the lack of agility of the quality systems.

Many sponsors and CROs do not have a clinical quality management system that is responsive enough to update the monitoring plan based on risk. Some of this is due to the common practice of CROs treating risk-based monitoring (RBM) as a more expensive line item or using it for only certain types of studies or clients. Additionally, the current state of quality systems includes technologies and other inflexible systems that create barriers to a more remote or virtual review

of data quality. Even if the standard operating procedures (SOPs) are general enough to support various site monitoring approaches, the actual trial execution, training, design, integration of technology, and differences in regional laws combine to create an unhealthy system.

In the long term, as pandemic conditions linger and we move into the reopening phases of trials, faced with increased expenses and the challenges with onsite monitoring, clinical research professionals need to ensure their quality management systems have the flexibility for the “new normal” for site management.

### **Risk-Based Monitoring**

Have you ever heard someone (maybe yourself) say, “We are not doing risk-based monitoring for this study”? This means that the monitoring function is conducting “traditional” monitoring. However, regulatory agencies, including the U.S. Food and Drug Administration (FDA), require sponsors to monitor the quality of their clinical investigations, and the [ICH E6\(R2\) Integrated Addendum](#) to the International Council for Harmonization’s guideline for Good Clinical Practice (GCP) made it clear that this includes ensuring that monitoring is based on risk.

So, if the choice is to do 100% SDV, that decision should be based on evaluation of risk. Remember, SDV is not monitoring the quality of the data; it only monitors the accuracy in the CRF. All studies should apply RBM or risk management in determining whether and how to perform remote monitoring. {1}

The term RBM is sometimes used as if it is a technique and a noun, instead of an action or standard foundation of a clinical quality management system. This disconnect starts early—usually during the selection of the study vendors. The request for proposal commonly inserts assumptions like “100% SDV,” which are then worked into the proposal by the vendor and get into the foundation of the relationship with the sponsor. This should be questioned at the pre-study stage, and it should have been occurring before the pandemic.

Many sponsors and CROs do not coordinate this well within the multiple layers of clinical organizations. Each stakeholder should complete this gap analysis as it moves into the post-COVID-19 landscape.



## Remote Monitoring Before COVID-19

So, what is your definition of remote monitoring? Is it part of centralized monitoring, or part of onsite monitoring prep and follow-up? Is it a separate activity?

The FDA and the European Union's (EU's) European Medicines Agency (EMA) released guidance to clarify remote monitoring before the pandemic. The FDA has for many years encouraged the use of various approaches to monitoring, including centralized monitoring and activities that review critical data offsite, when appropriate.

The FDA's 2013 guidance<sup>{2}</sup> on risk-based monitoring also clarifies some alternative monitoring techniques that could be done remotely, depending on the processes and systems in place. For example, 1) communication with sites, 2) informed consent form review, 3) informed consent process review, 4) original source data review, and 5) SDV could be done remotely. Many of these activities also require some review of the site's original source data remotely.

Besides centralized monitoring of data entered into the eCRF, remote access of source documents can be challenging due to privacy, system security, site time, unharmonized definitions of source data and certified copies across sites and sponsors/CROs, and unnecessary laborious processes, such as misusing the word "de-identify" vs. "redact."

In the EU, the [General Data Protection Regulation](#)<sup>{3}</sup> (GDPR) has some stringent rules for collecting or processing subject data, including during the conduct of a clinical trial. GDPR adds complexity to remote monitoring of source data by requiring that investigative sites pseudonymize source documents before sponsors/CROs receive them offsite. This would require additional onsite monitoring later to confirm attributability of the data to the study subject. Therefore, if 100% SDV is required, the value of remote SDV decreases. Remote monitoring does, however, have value globally for working with sites early to monitor quality performance.

GDPR is applicable for all businesses in the EU, but also to any business that is collecting or processing data of an EU subject. This applies to any study conducted in the EU. Regarding remote monitoring pre-COVID-19, if it is in line with national or local requirements, remote monitoring is limited to non-source document review. This includes, for example, discussions

regarding a trial subject's progress, issue management discussions, and training site personnel, but not SDV.

Globally, subjects need to know about any risks, safeguards, and rights they have regarding their data. For study participants, this includes the remote monitoring of their data, when applicable. Informed consents should be reviewed to ensure they support the requirements.

### **Remote Monitoring During and After COVID-19**

The practical implications of the restrictions and challenges during the pandemic are that sites can adjust to the new state of remote monitoring using a risk-based approach. The global guidance from regulatory authorities supports remote access for critical data during the restrictions. Has the current pandemic been a trigger to consider a risk-based approach and better support for remote monitoring? Is this true even in Europe?

The FDA guidance<sup>{4}</sup> for conducting clinical trials during COVID-19 restrictions supports remote monitoring for oversight of clinical sites. A risk-based decision should be made on what data are critical to monitor, while ensuring subject safety, data quality, and data integrity.

The EU guidance<sup>{5}</sup> for conducting clinical trials during COVID-19 notes in Chapter 11 (Changes to Monitoring) that “offsite monitoring” refers to remote communications between the site and sponsor, but this does not include remote SDV. Besides needing to be in line with current and temporary national law, the EU states that remote SDV can only be considered “during the public health crisis for trials involving COVID-19 treatment or prevention or in the final data cleaning steps before database lock in pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option.”

The remote review should focus on critical data, like primary efficacy data and important safety data. If secondary endpoint data can be assessed at the same time without asking for more source documentation and not adding to the site's workload, then that is acceptable during the crisis.

The EU guidance notes that remotely reviewed data will likely need re-monitoring, especially when the information has been de-identified and the review has been restricted to less data. De-



identified data or pseudonymized source data would require additional information to confirm identity at a later time. When using the word “redacting,” one must define the level of redaction, which does not necessarily mean at the level of de-identification. Following the regional, local, and institutional requirements must be ensured.

The interpretations of the EU guidance may ironically lead to more onsite monitoring after the crisis normalizes, depending on what the monitoring plans require for SDV. For global trials conducted in the U.S. and EU, this will require innovations to support more source data review (SDR, which we will discuss in a moment) and less SDV, as well as more remote monitoring of data.

Protecting the privacy, safety, and rights of study subjects is paramount. It is interesting that two regulatory agencies have such wide differences in the approach to remote site oversight. Is this due to SDV?

### **Telehealth and Remote Monitoring**

One global practice that has helped the industry during the pandemic is healthcare’s use of telehealth, also referred to as telemedicine, prior to COVID-19. In the U.S., the Office for Civil Rights (OCR) released an Enforcement Discretion<sup>{6}</sup> and a Frequently Asked Questions guidance<sup>{7}</sup> clarifying how telehealth may be used for remote healthcare visits during the pandemic. For clinical trials, subjects can have virtual visits through non-public videoconferences or home health services, when it is safe and feasible.

It has been observed that sites that are part of managed care using telehealth are more adaptable to performing clinical trial study visits using similar approaches as telehealth. Fortunately, the service providers’ telehealth platforms for managed care in the U.S. often have been vetted by the healthcare institutions for compliance with the Health Insurance Portability and Accountability Act (HIPAA). These institutions would need to consider the differences and risks in using video conferencing for remote study participant visits and for remote monitoring meetings between the sponsor monitor and the site’s research team vs. physician and patient

visits. In many cases, the sites and monitors can use video conferencing for remote visits with sites to discuss clinical trial participants' study cases.

GDPR allows telehealth under certain conditions{8}; the information must still be lawfully collected, which would be covered by the subject signing the consent to participate in the study and complete study visits, with permission for collection and processing of certain data. Additionally, the data are needed for compliance with regulatory authorities' requirements to monitor subjects' safety, for inspections, and for data retention.

Telehealth solutions need to meet the principles of GDPR:

- Lawful, fair, and transparent processing
- Purpose limitation
- Data minimization
- Accurate and up-to-date processing
- Limitation of storage in a form that permits identification
- Confidentiality and security
- Accountability and liability

Telehealth also needs to be compliant with any regional requirements under the ePrivacy Directive.{9} According to the statement{10} by the European Data Protection Board, only data that are necessary to complete the objectives should be obtained.

Given the requirements for protecting the rights of data subjects in the EU, telehealth for subject visits is more challenging and complex than in the United States, where the OCR released an Enforcement Discretion{11} for good faith disclosure of protected health information during the crisis. Telehealth may be employed more frequently, even after the crisis, and more guidance on how to proceed is likely to follow.

### **Remote SDR vs. SDV After COVID-19**

As previously noted, SDV involves reviewing original data or certified copies to check for accuracy in the transcription into the eCRF, while SDR refers to monitoring the quality of the

data, the compliance to the protocol, and the completeness of reporting subject safety. SDR may include some SDV. In the U.S. and EU, remote SDR can be performed when agreed upon between the sponsor and sites. When SDR involves SDV, it gets trickier and must meet national, local, and institutional restrictions for privacy.

There needs to be well thought out use cases related to what is acceptable for each sponsor and site based on their approved processes. For example, can a monitor ask a site's clinical research coordinator (CRC) to hold a paper source document in front of a screen during a video conference for the monitor to review? Can the CRC send a subject's lab value in the "chat" function for a monitor's review? Can a site attach a copy of a source document to an e-mail to the sponsor monitor?

In the EU, the EMA's guidance{12} for conducting clinical trials during COVID-19 states that remote SDV should be restricted per national and emergency measures to cases related to critical data and subject safety, which account for very few trials. They mention a few possible scenarios: *sharing pseudonymized copies of trial-related source documents with the monitor* that would likely require re-monitoring onsite later; *direct controlled remote access to subjects' electronic medical records (EMRs)*; and *video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.*

Sponsors and sites need restrictions in place regarding the use of the chat function and any recording of the session because of the risk of a breach of protected health information. Some examples of risks include a lab value and patient name being entered and sent to the monitor in the chat, or the monitor recording the session or taking screenshots of the source data during the session.

Both the sites and the sponsors/CROs should have processes in place to ensure subjects' privacy. For future trials, sponsors/CROs should include an assessment of the site's requirements related to remote communications regarding study subjects in site qualification visits. Sponsors should also ensure their processes for remote monitoring are flexible enough to support the variable restrictions from site to site, including using the site's approved technology vs. the sponsor's.

Should a site redact source documents before sending or making them available? Should a site provide direct access to the electronic source documents? How does the monitor document SDV remotely in the eCRF; does the eCRF system define the monitor's review the same as onsite? Each of these answers depends on the country, local, and institutional requirements of the site, sponsor, and vendors. Regardless, the sponsor has obligations to ensure it can review the quality of the documentation equally onsite and remotely. Ensuring the documentation meets the ALCOA standards is essential (i.e., the source documents are attributable, legible, contemporaneous, original, accurate, and complete).{13}

## **Conclusion**

As pandemic-related restrictions are lifted and onsite monitoring is permitted, reviewing that clinical sites have good documentation of their actions related to changes to their trials will become a top priority. Areas to focus on include documentation of consent, deviations related to changes, and documentation of communication with subjects (e.g., about home shipment of investigational product or protocol changes).

Remote monitoring and remote access to EMRs were possible before COVID-19 restrictions, but few thought about how best to implement them. The positive outcome and lessons learned from navigating through COVID-19 restrictions are that there can be a future with increased remote monitoring for clinical trials.

The industry needs to question whether tasks that are completed onsite are necessary, or if they are being completed onsite just because it is "how things are done." If a remote monitoring requirement is not part of the monitoring plan, it may be possible to challenge the norm. For example, remote investigational product accountability may initially not seem feasible, but there may be evidence of accountability with documentation, or video conferencing may provide another virtual solution.

It is likely that enough data will be gathered to support a continued progression to remote visits for subjects and remote monitoring, using a risk-based process to ensure quality clinical trials.

## References

1. ICH E6(R2) Guideline for Good Clinical Practice, Section 5.0, November 2016
2. U.S. FDA Guidance on Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring, August 2013
3. EU The General Data Protection Regulation 2016/679
4. U.S. FDA Guidance on Conduct of Clinical Trials of Medical Products During COVID-19 Public Health Emergency, March 2020
5. EMA Guidance on the Management of Clinical Trials During the COVID-19 (CORONAVIRUS) Pandemic Version 3, April 28, 2020
6. OCR Notification of Enforcement Discretion for Telehealth Remote Communications During the COVID-19 Nationwide Public Health Emergency
7. OCR FAQs on Telehealth and HIPAA during the COVID-19 nationwide public health emergency
8. Teleconsultation and COVID-19: who can practice remotely and how? Information for professionals practicing telehealth (telemedicine and telehealth), published on 18.03.20
9. Directive 2009/136/EC
10. Statement by the EDPB Chair on the processing of personal data in the context of the COVID-19 outbreak, March 16, 2020
11. OCR Notification of Enforcement Discretion under HIPAA to Allow Uses and Disclosures of Protected Health Information by Business Associates for Public Health and Health Oversight Activities in Response to COVID-19, March 30, 2020
12. EMA Guidance on the Management of Clinical Trials During the COVID-19 (CORONAVIRUS) Pandemic Version 3, 28/04/2020
13. ICH E6(R2) Guideline for Good Clinical Practice, Section 4.9.0, November 2016



**Sandra “SAM” Sather MS, BSN, CCRC, CCRA, FACRP**, is Vice President of Clinical Pathways, a consulting firm located in the Research Triangle Park area of North Carolina with a mission to promote clinical quality systems for sponsors/CROs and investigators/research institutions. She has been dual-certified by the Association of Clinical Research Professionals (ACRP) for more than 10 years (as both CCRC and CCRA). She also is a current ACRP Fellow, which is awarded to individuals who have made substantial contributions to the Association and the industry at large.



**Jennifer Lawyer, RN, BS**, is Operations Director at Clinical Pathways, with a focus on implementing processes to improve quality and on-time delivery for eLearning development and project management. Prior to joining Clinical Pathways, she was a private duty nurse and held other clinical research positions. She is an ACRP member and is working toward her professional certification.

SPECIAL FEATURE

## **The COVID-19 Effect: How to Maintain the Speed-to-Market Medical Model**

Astha Bhatia, BDS, MPH



In 1962, Dr. Frances Kelsey, who joined the staff of the U.S. Food and Drug Administration (FDA) two years prior, was honored by President John F. Kennedy for her refusal to rush approval to officially market a sleep aid called Kevadon<sup>®</sup> to U.S. consumers. Dr. Kelsey and her team at the FDA had fought furiously against pressure from the drug's would-be distributor, the Wm. S. Merrell Company, which assured the FDA that the drug was safe and effective. After all, it had been widely used throughout

other parts of the world since the mid-1950s as a sleep aid and as a potent agent against debilitating morning sickness suffered by pregnant women.

The company touted other positives for its product—it had passed animal testing; hundreds of doctors in the U.S. had already been given samples for research; and it was selling elsewhere at a low cost and without a prescription. In Merrell's view, Dr. Kelsey was simply being stubborn and obstructive.

Today, it is well known that Dr. Kelsey's steadfast position saved an untold number of women in the U.S.—though not all—from giving birth to severely deformed infants. Kevadon's ingredient, thalidomide, was identified in 1961 as the culprit of horrible birth defects in possibly tens of thousands of infants born throughout Europe and parts of Africa.

Having earned recognition for her significant contribution to the health and well-being of the public, Dr. Kelsey spent another 43 years at the FDA, primarily in the area of drug testing and establishing policies that strengthened the processes for releasing drugs and medical products to consumers. After 1962, drug makers had to demonstrate the safety and efficacy of their products by way of “substantial evidence” and include “adequate and well-controlled clinical studies.” Manufacturers were also forbidden to market their products until they were given the green light to do so by the FDA.

In fact, restrictions were so strong and statutes so complex that the FDA eventually came under fire for being too slow to approve new medications. In 1997, Congress passed the Food and Drug Administration Modernization Act in an attempt to hasten the agency’s review and approval of new medical treatments.

### **Then Came COVID-19**

Fast-forward to May 2020, when the FDA took more unconventional and situational steps to accelerate the investigation and development of prevention and treatment therapies for COVID-19 in light of the urgency surrounding the pandemic.

Publishing a series of guidance documents, the FDA provided researchers and “innovators” with a roadmap for hastening the development of new drugs and biological products, and for conducting clinical trials to determine their safety and efficacy. This action followed earlier steps the FDA took to work with federal agencies, academic institutions, and drug manufacturers to accelerate medical solutions to the virus, including the launch of the Coronavirus Treatment Acceleration Program (CTAP).

The CTAP is an emergency-access program that administers potential coronavirus treatment options to patients. It provides subject-matter expertise to the COVID-19 treatment-acceleration program launched in April by the Foundation for the National Institutes of Health (FNIH) called Accelerating COVID-19 Therapeutic Interventions and Vaccines, or ACTIV.

The FDA and FNIH are just two of the federal agencies that have joined forces with one another and with private partners from academia, philanthropic organizations, and pharmaceutical

companies to collectively prioritize coronavirus tests, treatments, and/or vaccines, applying all available resources to rapidly thwart the pandemic.

Now, questions are beginning to arise. Having heard concerns that the FDA might be moving too quickly on a vaccine, FDA Commissioner Dr. Stephen Hahn in early August assured members of the American Medical Association that the FDA will not compromise safety while rushing approval for a vaccine for the novel coronavirus. “All of our decisions will continue to be based on good science and the same careful deliberative processes we have always used when reviewing medical products,” Hahn said, adding, “We all understand that only by engaging in an open review process and relying on good science and sound data can the public, and you as providers, have confidence in the integrity of our decisions.”

Hahn said he can’t predict when the results will be ready, but large-scale clinical trials have already been initiated on several vaccine candidates, some in less than six months after the virus was detected.

### **What is the Right Timing?**

The speed of drug development is controversial, and no one can prescribe the appropriate timeline for the approval of any drug; what matters most is a drug’s safety and efficacy. Can the public be assured that a cure won’t be worse than its targeted disease? Will the drug accurately and efficiently do its intended job? Can testing move any faster? Should we commit to take the time needed for 100% certainty about the drug’s viability?

To be sure, COVID-19 has proven that there is potential to streamline the clinical research process, but the solution lies in getting health authorities to coordinate and interact with each other to reduce the duplication of efforts—not to eliminate any step in the efforts.

What is needed is a global consensus on study protocol requirements, supporting documentation, and application forms to avoid country-level discrepancies. If researchers were allowed to fill up a centralized application and add some country-specific documentation, the paperwork and time needed to get the research started would be reduced. In other words, it’s the administrative functions, not the research itself, that need to be expedited.



## **The Devil is in the Documentation**

Multiple regulations exist for clinical research across different health authorities, medical associations, and ethics committees throughout the world. Researchers must get all the approvals and complete the required documentations for each prior to initiating any clinical trial. While these regulations were introduced to protect the safety of the study subjects, the number of regulations has increased significantly in recent times and at varying levels.

Further, because health authorities across the globe do not usually interact with each other, getting research started typically takes a long time—often to the detriment of study subjects and the prospective patient population. Yes, it is imperative that clinical research follows proper regulatory guidelines; however, most often these guidelines are complex and disjointed between the various health authorities and countries.

Each country has its own applications to complete, forms to fill out, and guidelines to adhere to. The approval process, thus, is long and, due to the constantly overburdened system, clinical trial applications may take months to be reviewed by each health authority. This is followed by the ethics committees' reviews, which further take time.

For every new clinical trial, a researcher must follow the nuances of guidelines of each individual country, but those guidelines exist on a splintered continuum, burdening what could be a more streamlined process if there were a central entity accepting and processing the relevant forms and documents.

Often, researchers develop what can be called a culture of fear, worrying about the added cost of filling out these multiple, global applications and going through the added red tape. This is detrimental to bringing new and novel treatments to the patients.

Sometimes, some patients, specifically certain cancer patients, do not have long to live and waiting too long to complete the massive paperwork might deprive these patients of these promising newer treatments. In the most extreme cases, the medical community has witnessed some researchers going out of the U.S. to locations with less-stringent regulations or faster

processes to perform their clinical research, hoping for a more rapid outcome that could heal a particularly stubborn illness or even save a life.

### **Examples of Steps to Streamline**

It's worth noting that the FDA has taken many steps in the past to work with global partners in streamlining drug testing and clinical trial processes, including:

- In 2009, the European Medicines Agency (EMA) and the FDA agreed to collaborate on international Good Clinical Practice inspection activities. In short, the intent was to safeguard clinical trial subjects as clinical research grew more global.
- In 2013, the same two organizations announced an initiative to conduct joint-facility inspections for generic drug applications submitted to both agencies.
- In the fall of 2019, the FDA worked collaboratively with Canada and Australia to develop Project Orbis, a framework allowing concurrent submission and review of oncology products for patients with endometrial carcinoma.

The question then becomes, what is being done globally to streamline clinical research processes? Can there be a globally centralized process for initial protocol approvals? How can we keep countries' timelines in sync so that there can be more collaboration from one country to another using the same documentation so that the process is simpler and faster?

### **COVID-19 Again Becomes the Model**

In March, the World Health Organization (WHO) created the Solidarity trial, a global effort to rush clinical testing of four potential COVID-19 treatments:

- The anti-malarial drugs chloroquine and hydroxychloroquine (which have since been eliminated from the trial due to ineffectiveness);
- the HIV drugs ritonavir and lopinavir;
- the anti-viral drug remdesivir; and
- a combination of ritonavir and lopinavir with Interferon- $\beta$ , an immune-system regulating protein.

As of July 2020, some 5,500 patients had been recruited for Solidarity from 21 countries; more than 100 countries expressed interest in joining the trial. WHO Director General Dr. Tedros Adhanom Ghebreyesus said the goal of the Solidarity trial is “to dramatically cut down the time needed to generate robust evidence about what drugs work” against COVID-19.

The advantage here is that these drugs already have a history of effectiveness in treating other maladies; their safety is under less scrutiny than would be if that were not the case. However, it stands to reason that given a similarly centralized and streamlined “clearing house” for initial protocols, documentations, timelines, etc., countries throughout the globe could reduce the time needed for new clinical research trials.

For certain commissions, some bureaucracy could be set aside in the interest of collaboration. Let’s not bury the most promising of drugs deep into the layers of red tape, but rather bring them to the market as soon as possible.

### **Something Good to Come from COVID-19?**

It’s remarkable how effectively government agencies and private organizations have banded together during this COVID-19 pandemic to speed the process for researching, developing, and implementing potential treatments to fight the virus. It begs the question: Why were such dire circumstances required to bring such changes about?

Clearly, the traditional system for bringing therapies to the market is burdened with restrictive rules and regulations and conflicting schedules that actually work to slow the processes. Now that there is proof the system can be streamlined, all parties involved in the efforts against this pandemic need to work together so that this is not the exception, but rather the rule for moving forward on other medical products for the benefit of patients.



**Dr. Astha Bhatia, BDS, MPH, ([drasthabhatia@gmail.com](mailto:drasthabhatia@gmail.com))** is an expert clinical scientist in the field of hematology and oncology, a dental surgeon, and a public health professional. She is passionate about bringing newer and more effective treatments to cancer patients and promoting community public health. For more information, please contact her via e-mail or LinkedIn ([www.linkedin.com/in/drasthabhatia](https://www.linkedin.com/in/drasthabhatia)). Her article was contributed to ACRP through [Trade Press Services](#).

RECRUITMENT & RETENTION

## **RACE for Children Act Aims to Improve Pediatric Cancer Care**

Lynne Georgopoulos, RN, MSHS, RAC; S. Y. Amy Cheung, PhD



Approximately 1.8 million new cases of cancer will be diagnosed in the U.S. in 2020.<sup>{1}</sup> Less than 1% of them will be diagnosed in pediatric patients.<sup>{2}</sup> Although pediatric cancer is rare, it is the second leading cause of death in children ages 1 to 14 in the U.S. after accidents, and the number of cases are steadily rising.<sup>{2}</sup>

It is a complex situation; there are more than 100 types of pediatric cancer, and their distribution varies by age.

For example, the incidence of leukemias in children 1 to 4 years of age is more than twice that in adolescents (15 to 19 years of age).<sup>{3}</sup> In contrast, lymphomas rarely occur in children younger than 4, but comprise about a quarter of all cancers diagnosed in adolescents.<sup>{3}</sup>

While there are hundreds of approved cancer therapies, only about 40 have pediatric labeling, and only four have been developed specifically for pediatric cancer.<sup>{4,5}</sup>

### **RACE for Children Act**

The Research to Accelerate Cures and Equity (RACE) for Children Act aims to advance more effective therapies for pediatric cancers.

The RACE for Children Act was incorporated as Title V in the 2017 U.S. Food and Drug Administration (FDA) Reauthorization Act and just went into effect on August 18 this year. It builds upon earlier advances made by the Pediatric Research Equity Act (PREA) and the Best

Pharmaceuticals for Children Act (BPCA), which resulted in more than 800 medicines being labeled for pediatric use but had limited success with oncology drugs.

PREA was previously only triggered by an application for a new indication, dosage form, dosing regimen, route of administration, or active ingredient, unless the drug was for an indication with orphan designation. The RACE for Children Act amends PREA and requires the sponsor of an *original* New Drug Application (NDA) or Biologics License Application (BLA) for an adult cancer drug directed at a molecular target considered relevant to the growth or progression of a pediatric cancer to submit an initial Pediatric Study Plan (iPSP).

The Act applies to NDAs and BLAs for a new active ingredient, which may include biosimilars, filed on or after August 18, 2020. It applies even if the adult cancer does not occur in children or the adult indication was granted orphan designation.

The iPSP must contain an outline of the proposed molecularly targeted pediatric cancer investigation, “using appropriate formulations, regarding dosing, safety and *preliminary efficacy* to inform potential pediatric labeling.”{6} It should also include any planned request for a deferral or waiver together with supporting documentation.

Sponsors should leverage adult safety, pharmacokinetic (PK), and efficacy data to inform pediatric trial design and assess whether an age-appropriate pediatric formulation is required. The iPSP needs to be submitted to the FDA within 60 days of the end-of-Phase II meeting,{7} and it will take about 210 days to receive either an agreement or a non-agreed letter.

The iPSP must address the following areas:

- **Safety:** Determine tolerability and dose limiting toxicities in pediatric patients
- **Exposure:** Examine PK across different age groups as appropriate
- **Dose/Exposure/Response (DER):** Support the pediatric recommended Phase II dose (RP2D)
- **Response:** Assess the overall response rate across the entire study population in biomarker enriched population(s), pre-specified disease cohorts, or adaptive design settings
- **Sample Size:** This will vary, but should support the study objectives

As this is a new regulatory requirement, sponsors might want to consult the relevant guidance{8} and FDA’s lists of relevant and non-relevant pediatric molecular targets.{9} As these target lists are not binding, requesting a consultation with the Oncology Center of Excellence Pediatric Oncology Program and the Oncology Subcommittee of the Pediatric Review Committee might be valuable.{10} Requesting scientific advice from the FDA and European Medicines Agency (EMA) in tandem could also help avoid the need for duplicate pediatric studies. FDA also suggests that sponsors consider including adolescents in Phase II trials, which is a practice employed in other therapeutic areas.

### **Pediatric Challenges**

Working with pediatric populations is complicated, because children are not small adults. Rapid changes due to growth and maturation, impact body composition, organ size, PK processes (such as absorption, distribution, metabolism [enzymes and transporters], and elimination), and pharmacodynamic (PD) processes (such as receptor responses).{11}

There are also practical and ethical reasons why it is not possible to collect all the requisite pediatric data from clinical trials. Overcoming these challenges requires the application of a quantitative framework that can use sparse pediatric samples or existing adult and pediatric data from drugs in the same class—or a similar class of compounds—to build a more complete picture of the new drug’s activity.

In addition, sponsors need to leverage all the available real-world and published clinical data to bridge knowledge gaps between adult and pediatric patient populations and understand the extent of disease similarity and, if different, the magnitude of disease progression or DER relationship.

### **Model-Informed Drug Development (MIDD) Benefits**

MIDD approaches,{12} which have been widely adopted by global regulatory agencies including the FDA, the EMA, and Japan’s Pharmaceuticals and Medical Devices Agency, can help to achieve those goals. Population PK models can employ allometric scaling using body size metrics to scale adult data for pediatric purposes and support the optimal starting dose and schedule selection for the first pediatric trial.

Physiologically based PK (PBPK), which incorporates ontogeny, physiological changes, and disease progression, can be used to model drug performance, assess drug-drug interactions, simulate responses for different age groups, and conduct adult-to-pediatric extrapolations. MIDD can also support dose optimization, provide evidence of efficacy, improve clinical trial designs, and reduce the size or eliminate the need for clinical trials in certain circumstances. These quantitative MIDD strategies make optimal use of all the existing data and help sponsors to prepare the requisite elements for their iPSP efficiently.

## Conclusion

Pediatric oncology patients need safer, more effective therapies. It is anticipated that the RACE for Children Act will help to make that goal a reality. When successfully applied, MIDD can support dose optimization, identify risks and benefits of the drug product under development, improve clinical trial efficiency, and reduce the burden of trial participation to enhance patient recruitment and retention, with the goal of increasing the probability of regulatory success.

## References

1. American Cancer Society. Cancer Facts & Figures 2020.  
<https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf>
2. American Cancer Society. Key Statistics for Childhood Cancers.  
<https://www.cancer.org/cancer/cancer-in-children/key-statistics.html>
3. Source SEER Cancer Statistics Review 1975–2017, Table 29.1.  
[https://seer.cancer.gov/csr/1975\\_2017/browse\\_csr.php?sectionSEL=29&pageSEL=sect\\_2\\_9\\_table.01](https://seer.cancer.gov/csr/1975_2017/browse_csr.php?sectionSEL=29&pageSEL=sect_2_9_table.01)
4. Coalition Against Childhood Cancer. Drug Development Section.  
<https://cac2.org/interest-groups/awareness/childhood-cancer-fact-library/>
5. Ye J. 2019. Statistical and Regulatory Considerations on Registration Trials in Pediatric Cancer (PowerPoint) The 3rd Stat4Onc Symposium.  
[https://events.stat.uconn.edu/stat4onc/talk-slides/April27-1030-1200/Jingjing\\_Ye\\_Stat4Onc\\_2019.ppt](https://events.stat.uconn.edu/stat4onc/talk-slides/April27-1030-1200/Jingjing_Ye_Stat4Onc_2019.ppt)
6. FDARA Title V Sec 504 (a)(3)(A) or Federal Food, Drug, and Cosmetics Act (FD&C Act) Sec. 505B (a)(3)(A).
7. Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans Guidance for Industry. 2020.  
<https://www.fda.gov/media/86340/download>

8. U.S. Food and Drug Administration. 2019. Draft Guidance: “FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry.”  
<https://www.fda.gov/media/133440/download>
9. U.S. Food and Drug Administration. Pediatric Molecular Target Lists.  
<https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>
10. U.S. Food and Drug Administration. 2020. FDA Oncology Center of Excellence. Pediatric Oncology Product Development Early Advice Meeting (Type F)1,  
<https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology-product-development-early-advice-meeting-type-f1>
11. Corriol-Rohou S, Cheung SYA. 2019. Industry Perspective on Using MIDD for Pediatric Studies Requiring Integration of Ontogeny. *Clinical Pharmacology*.  
<https://accp1.onlinelibrary.wiley.com/doi/full/10.1002/jcph.1495>
12. EFPIA MID3 Workgroup. 2016. Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation. *CPT Pharmacometrics Syst Pharmacol* 5(3):93–122. <https://pubmed.ncbi.nlm.nih.gov/27069774>



**Lynne Georgopoulos, RN, MSHS, RAC**, is Vice President of Regulatory Strategy at [Certara](#) and a founding member of the company’s Pediatric Practice, which provides integrated drug development, regulatory strategy, population PK modeling, and PBPK analysis with the Simcyp® Pediatric Simulator. Certara has contributed to more than 100 Pediatric Investigation Plans and Pediatric Study Plans.



**Amy Cheung, PhD**, is Senior Director of Integrated Drug Development at Certara and a project manager and core group member of the company’s Pediatric Practice. She has expertise in pediatric drug development, oncology trials, MIDD, PBPK, and extrapolation. She is a member of the IQ CPLG pediatric working group and co-chair of the TALG CPLG Pediatric PBPK group.



## **Innovations are Expanding the Possibilities for Addressing COVID-19**

Al O. Pacino; Yonnie Otieno



*International efforts to curb the spread of COVID-19 have been on the rise. As a result, a focus has been put on the need for the discovery of lifesaving treatments and prevention. Cooperation between governments, biotechnology companies, and the scientific community has led to a greater understanding of the importance of modern clinical trials.*

### **Unlocking Treatment Drugs, Vaccine Prospects, and New Testing Kits**

COVID-19 cases globally are currently managed by a variety of treatments, including repurposed existing drugs and drugs that are still in experimental stages of development. Antimalarial, upper respiratory antibiotic, and antiviral treatments have all been administered in some cases on a compassionate basis for the disease. At the same time, scientists are collaborating with government labs, biopharmaceutical companies, and academic medical centers to start enrolling patients into clinical trials.

Clinical studies on the SARS-CoV-19 virus pathogenesis can provide insights for test kit development, and on the complex immunological mechanisms of vaccine candidates that may ultimately stop COVID-19 transmission. Historically, the success of other vaccines for various conditions have led to our understanding of antibodies as an indispensable component for combatting highly contagious diseases through medicine and biomedical research.

The COVID-19 blood plasma antibodies, specifically IgG and IgM, fight and eventually neutralize COVID-19. Naturally, antibodies protect us from diseases and re-infection transmissions. Interestingly, the causative relationship between microbes and diseases was first studied in Germany in 1884 by two great scientists, Robert Koch and Friedrich Loeffler, who postulated the disease process as a cell-based phenomenon.

IgG and IgM antibodies provide the silver lining answers to this latest pandemic. Antibodies fight diseases and the cell keeps a memory of the specific invading protein's antigens. Similarly, blood plasma from a donor who has fought off infection (convalescent plasma) can be passively exchanged in order for another person to gain protective antibodies for COVID-19. The effectiveness of such donated plasma is achieved by the mimicking of vaccination principles by which neutralizing antibodies are released to defend the body and confer immunity to an invading virus.

From 2014 to 2016, during the Ebola epidemic, three West African nations—Liberia, Sierra Leone, and Guinea—rolled out convalescence plasma antibodies from Ebola virus survivors as a treatment option. Right now, clinical trials are again looking at safety and efficacy protocol of COVID-19 convalescent plasma.

### **Hybrid Trials and the Modernization of Clinical Trials**

In this extraordinary time, the biopharma and medical device wings of the industry are coming together to develop vaccines, new prophylaxis drugs, and accurate test kits options. After preclinical activities, the next stage is to quickly identify a network of sites for trials. We should be able to use highly valuable digital applications to connect, pick, and choose sites of excellence.

It is also becoming necessary, with social distancing being followed, to apply a range of both virtual and non-virtual digital options for monitoring and advancing telemedicine care tools in clinical research. Hybrid clinical trials ought to share and exchange regulatory information for business purposes, but also require modern digital systems that efficiently implement mandatory quality assurance management.

Bureaucratic hurdles can be mitigated with the support of robust regulatory and proficiency systems for all training standards and clinical compliance. Altogether, the net result can be the elimination of fraud, waste, and abuse in the healthcare and clinical research processes. A credible third-party institution oversight locally trusts and verifies all applications at the source.

For sponsors, quickly connecting to a global network of sites for either centralized or decentralized clinical trials offers opportunities for partnerships with hybrid clinical trial service providers. Meanwhile, project managers need to be able to deliver trainings, quality operating standards, protocols, and tracking for reliable clinical results to follow. Overall, updated clinical trial processes can lead to the expediting of human subject protections for institution-based and online enrollments into studies.

### **The Next Milestone**

As with any other healthcare product, designing effective testing kits and the clinical trials for evaluating them takes time, but it is essential for new COVID-19 tests to meet the tenets of biomedical Good Manufacturing Practice before such equipment can be marketed. In the meantime, stakeholders need to stress the international cooperation that can be achieved through technology-based, hybrid clinical trial models that are designed to ensure patient safety and adherence to Good Clinical Practices.

Regulatory authorities such as the U.S. Food and Drug Administration and European Medicines Agency oversee registration and use of prophylaxis or vaccines and medical devices, but the current evaluation time for this process must be reduced. A post-COVID-19 future is possible in which breakthroughs will continue to unfold as public benefit organizations, governments, private industry, and nonprofit organizations collaborate on scales rarely, if ever, seen before.



**Al O. Pacino** is President at BlueCloud® by HealthCarePoint Professional Collaborative Networks, based in Cedar Park, Texas, and a former member of the Editorial Advisory Board for ACRP.



**Yonnie Otieno** is Manager at BlueCloud® Africa by HealthCarePoint Professional Collaborative Networks, based in Nairobi, Kenya.

## SITE STRATEGIES

### **Transparency is the Right Tactic With Your Site Staff, Too**

Elizabeth Weeks-Rowe, LVN, CCRA



A standard discussion topic during site evaluation visits is that of regulatory audits, and the leaders and staff at most research-savvy investigational sites that have experienced an audit by the U.S. Food and Drug Administration (FDA) are typically prepared to discuss the related circumstances and outcomes. There are exceptions; a complicated audit circumstance can fluster even the most prolific researcher, while an inexperienced clinical research coordinator (CRC) may not yet have developed a deep enough perspective on what happened to provide commentary.

Overall, audit-focused discussions are transparent and facilitate critical understanding during the site evaluation process. Once, however, I conducted an evaluation with a new CRC who reacted uncomfortably to the topic of regulatory audits, which baffled me.

While researching the site to prepare for the evaluation visit, I discovered the site’s principal investigator (PI) had been previously audited by the FDA. This CRC was unfortunately affected by circumstances that preceded her employment, and for which she bore no responsibility. None of her colleagues had objectively explained the audit process to her, and negative perceptions had taken root in her impressionable mind.

Hesitation hovered uncomfortably before landing on the inevitable answer—“Yes.” The CRC sighed as she responded. Yes, the site had been issued a 483 (Warning Letter) because of the audit.

Her follow up question—“Isn’t that bad?”—gave me pause.

## **They Don't Know What They Don't Know**

The CRC should never have had this situation forced into her assimilation to clinical research. The standard feelings that accompany any learning process—enthusiasm, worry, struggle, accomplishment—should create a cycle forming competency and, ultimately, confidence. It is critical to nurture that confidence with information grounded in facts and transparency, not swathed in a negative aura of looming consequence. Negative perceptions like the one this CRC had developed, if not righted, will limit understanding.

I informed her that the final decision regarding the audit findings was contingent on data analysis. It was not as simple as “good” or “bad.” I explained that each audit circumstance and outcome demanded individual consideration of audit details, findings, and site responses when forming the fundamental conclusion.

This was a valuable teaching moment I could not ignore, for it was an opportunity to allay her misgivings and provide an objective perspective. I explained that 483s were issued for a variety of reasons and levels of gravity; all reports were considered in the site selection process. My explanation included the vast number of good sites I had evaluated who had been issued 483s, but were still awarded studies as the pharmaceutical company objectively considered each case and took into account such factors as the significance of the findings, the audit history and timeframe, and others.

I continued by explaining that the common element among experienced, competent investigational sites that had been issued 483s from an FDA audit was the quality of the PI's response to the agency. When clarity, transparency, consistency and follow through framed the site audit response, an effective dialogue toward resolution was fostered.

The smartest PIs saw the 483 as an impetus for change, or an opportunity to clarify/correct deviations, or even demonstrate an audit finding error. The corrective action resulting from audit findings included new or improved standard operating procedures for critical research process such as informed consent, safety/adverse event (AE) reporting, drug accountability, training

practices, investigator oversight, and data collection. These standardized processes help research staff execute clinical trials consistently according to Good Clinical Practice standards.

It was impossible to summarize the importance of objectivity when considering audit findings in a 30-minute conversation. All I could hope was that my explanation shifted the CRC's undue concern.

### **We All Need a Wake-Up Call Sometime**

The most memorable investigational site responses to audit findings reflect the benefits to site transparency and transformations in research processes that can result from audits.

I once visited a small specialty practice to discuss an impending cardiology study. The study coordinator (Linda) was cordial and not at all uncomfortable discussing an earlier audit and 483 at the site. Her candor was instrumental in clarifying the chain of events that brought her to the site and the actions wrought to change the site paradigm.

She explained that after a sponsor audit of a high-enrolling study had uncovered some discrepancies with patient eligibility, her PI decided to conduct an internal audit that revealed some questionable data practices by an earlier CRC. Soon after that CRC left the site, the PI began searching for a more experienced replacement, having realized that he had neglected study oversight by over-delegating study activities to sub-investigators and placing too much responsibility with the CRC. Upon her arrival, Linda and the PI cleaned up the site's studies and reported the deviations/issues to the respective sponsors, which resulted in the FDA audit.

The unfortunate circumstances were the impetus for immediate and dramatic changes at the site. The PI moved his research clinic, previously located several miles away, to his medical practice location. This reinforced his commitment to PI oversight and patient safety. He participated in every patient consenting process to ensure CRCs' and participants' understanding of everyone's rights/responsibilities in the study.

This PI was also involved in every patient screening visit—verifying and signing off on every inclusion/exclusion criterion. He downsized to only one sub-investigator. He added a full-time

research assistant/backup CRC to ensure Linda had a manageable workload. The PI and his research department met twice weekly to discuss study/patient status, monitoring visit findings, and the study pipeline.

The PI further encouraged the CRCs to become certified and covered their initial examination fees and continuing education costs. Together, they developed and documented harmonized policies for research tasks such as informed consent, AE reporting, and study drug accountability/storage.

This site's response to adversity was to elevate study conduct and ensure patient safety/data quality. The wake-up call became its defining moment. Its transparency rebuilt the trust integral to solid sponsor/investigator relationships.



**Elizabeth Weeks-Rowe, LVN, CCRA,**

([elizabethwrowe@gmail.com](mailto:elizabethwrowe@gmail.com)) is a former CRC who now works in site selection and education in the contract research organization industry. She last wrote for *Clinical Researcher* in June 2020's "[Is Your Site's CRC Training Methodical or 'Trial by Fire'?](#)"