

# Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

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**Rethinking Risk, Race, and Other Urgent Issues in Clinical Research**

## Clinical Researcher™

### Association of Clinical Research Professionals

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EXECUTIVE DIRECTOR'S MESSAGE

## **The Urgency of Diversity**

Jim Kremidas



The clinical trials industry has struggled with finding effective ways to advance diversity in its participant population for decades. While there are glimmers of improvement here and there, it has remained a stubborn challenge, and even optimists don't claim we are on the verge of solving it in a significant way. However, I don't need to tell you how important it is for clinical trials to better represent the people the medications, treatments, and devices are designed to help.

ACRP and its members applaud efforts to promote diversity in patient populations, but we also believe our industry is overlooking an important issue if we fail to address the relative lack of diversity in the clinical trials workforce itself. We all know a high percentage of first-time clinical trial participants learned about an opportunity from a physician or other healthcare worker. It stands to reason that a clinical research workforce that is more representative of all patient populations would be an effective way to promote diversity in those who choose to participate in trials.

In the rest of this column, I'll highlight some of the ACRP initiatives that aim to change the face of the clinical trials workforce in urgent and progressive ways.

## **Find Your Element**

Earlier this year, ACRP's [Partners in Workforce Advancement](#) (PWA) launched "[Find Your Element](#)"—a digital advertising campaign to raise awareness of the clinical research profession among a diverse population of college students. The PWA is a multi-stakeholder collaborative initiative with goals for growing a diverse clinical research workforce, setting and supporting standards for workforce competence, and supporting site sustainability of research sites.

The workforce outreach campaign was piloted at several colleges and universities in the Research Triangle Park region of North Carolina and in Miami, Fla. It aimed to expand awareness of clinical research as a profession among nearly 400,000 college students in the pilot phase alone, and engaged at least 50,000 students directly in one form or another.

Featuring advertising messages in both English and Spanish, the campaign highlights key reasons students from all ethnic and cultural backgrounds can "find their element" in clinical research.

While we don't yet have hard metrics, I can tell you we've been very encouraged by the campaign's progress on an anecdotal level. In fact, in June we expanded the initiative to three new major U.S. markets: Minneapolis-Saint Paul, Greater Houston, and New Hampshire (including Boston).

## **The Bigger Picture**

I'm very excited about the PWA and ACRP's opportunity to help bring together some of the most important people and institutions in clinical research to tackle such critical issues as advancing diversity in the profession and raising the quality of clinical trials. In early June, representatives of the U.S. Food and Drug Administration, National Institutes of Health, Dartmouth-Hitchcock Health, Society for Clinical Research Sites, and the Center for Information and Study on Clinical Research Participation joined together as the PWA Executive Steering Council.

ACRP's PWA now includes more than 25 organizations aligned with ACRP's mission and working to improve clinical trial quality and outcomes for patients by focusing where others have not—on workforce planning, development, and assessment.

The Partners in Workforce Advancement Executive Steering Council includes:

- Leigh Burgess, Vice President for Research Operations, Dartmouth-Hitchcock Health, ACRP's Elite Partner in Workforce Advancement
- David Burrow, PharmD, JD, Director, Office of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- Kenneth A. Getz, Founder and Board Chair, Center for Information and Study on Clinical Research Participation
- Michael G. Kurilla, MD, PhD, Director, Division of Clinical Innovation, National Center for Advancing Translational Sciences, National Institutes of Health
- Allyson Small, Chief Operating Officer, Society for Clinical Research Sites

### **All That's Missing is More of You**

As always, I encourage you as an ACRP member to become a bigger part of our industry by volunteering and sharing your knowledge. If you'd like to learn how to contribute, or have any thoughts about ACRP's mission and activities, please reach out to me at [jkremidas@acrpnnet.org](mailto:jkremidas@acrpnnet.org).

**Jim Kremidas** is Executive Director of ACRP.

CHAIR'S MESSAGE

## Clinical Research's Carpe Diem Moment

Paul Evans, PhD



There aren't many good things to say about COVID-19, of course, but I'm heartened to see how it has demonstrated the importance of clinical research in the media and helped the general public recognize clinical trial practitioners as the front line heroes they truly are.

As an industry, I believe we've been given an opportunity to expand clinical research beyond the pandemic. There has been a lot of talk about what the new normal post-COVID might look like. Virtual studies are getting a lot of coverage, but potentially there is a much bigger shift on the horizon if we are able as an industry to seize the initiative. I'm talking about patient awareness and recruitment.

We all know one of the biggest barriers holding back clinical research is finding new patients for clinical trials. Lack of awareness in the population of what clinical trials are and why they are so important is a big contributor to the problem.

That was then, and this is now. COVID-19 has put clinical research and clinical researchers on the map. We even see study volunteers being interviewed on CNN—you could even say clinical trials are sexy!

As the first Phase III vaccine trials for COVID-19 get under way, you can already see the impact. My own firm is involved in several of these studies at multiple sites, and what I've observed is very encouraging. For the first time in my 30-year career, patient recruitment is not a problem. Patients are almost lining up to take part.

The question is, can we as an industry take advantage of this new-found excitement for what we do, or will we squander this chance with a “back to business as usual” mentality as COVID-19 fades from memory? Are we ready to more proactively—and transparently—engage patients, or will as an industry revert to type and become excessively secretive again? Of course, there are often good reasons for keeping commercially sensitive information confidential, but are we too prone to secrecy for secrecy’s sake?

If we are more open with the population at large, it will:

- Build trust and encourage more people to take part in studies.
- Engage people in the mission—more and better drugs for more patients in need.
- Make us enablers of participation.

Another major infectious disease crisis that caught people’s attention was AIDS. We found then that the public will find a way to acquire and share information—and the social media as we know them now weren’t even available then.

COVID-19 is a horrific crisis, no doubt about it, but it’s given our industry a real opportunity to shine today, tomorrow, and beyond. It’s up to us as clinical trial practitioners to seize the day as we find new ways to engage with patients and harness their new enthusiasm for our shared work to alleviate suffering and save lives.

**Paul Evans, PhD**, is President and CEO of Velocity Clinical Research, and Chair of the Association Board of Trustees for ACRP in 2020.



PEER REVIEWED

## **The Critical Need for Transparency and Disclosure of Participant Diversity in Clinical Trials**

Yaritza Peña; Zachary P. Smith; Kenneth A. Getz, MBA



It is well known that the underrepresentation of minority groups in clinical trials decreases the generalizability of clinical trial findings by disguising the potential effects of variation in the pathobiology of disease and race-related differences in drug responses. As a result, several regulatory policy initiatives have focused on developing clinical trial enrollment practices that improve the inclusion of diverse patient subpopulations.

The U.S. Food and Drug Administration (FDA) first released guidance about the importance of studying the effects of products in elderly patients in the 1980s.<sup>{ 1 }</sup> A decade later, the agency issued a “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” and established the Office of Women’s Health. Despite the progress made as a result of these guidance documents, underrepresentation of racial and ethnic minorities in clinical trials remained highly prevalent.

In 2012, the U.S Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA) to address ongoing concerns over the lack of diversity and representation in clinical trials. Section 907 of the Act calls for the FDA to improve the inclusion and transparency of clinical trial data representing demographic subgroups.<sup>{ 1,2 }</sup> In 2013, a cross-agency task force involving representatives from the Office of the Commissioner, the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and

the Center for Devices and Radiological Health (CDRH) found that the FDA’s statutes, regulations, and policies generally provided product sponsors a solid framework for disclosing data on the inclusion of demographic subgroups in their applications.{ 1 }

In 2014, the FDA responded with a new annual publication called “Drug Trial Snapshots.” This publication routinely discloses the extent to which Section 907 of the FDASIA is applied in biomedical research; the print and online versions present the demographic distribution of participants in clinical trials of approved New Molecular Entities (NMEs) for that given year as well as any observed differences in safety and efficacy by demographic subgroup.

Conclusions regarding these differences, however, cannot always be made from the Snapshot reports alone. The data they provide are limited to individual years, thwarting researchers from evaluating trends in participant subgroup demographics.

Aside from FDA recommendations, there are no regulations currently in place that require industry sponsors to include women and minorities in their trials and no programs that provide insight into missing data.{ 3,4 } Perhaps most importantly, current guidance documents do not disclose the information necessary to assess disparities in demographic diversity given individual disease prevalence rates.

### **What We Need Versus What We Have**

More comprehensive data on participant demographic subgroups may aid clinical research professionals in identifying opportunities to improve diversity in their research sites. Specifically, it can help to identify the areas of greatest need, including where demographic subgroup disparities are the greatest, both overall and within specific therapeutic areas or disease conditions.

The information can also be used to assess how participant diversity has changed over time. The availability of results may promote innovations in clinical trial design and avoid duplication of unsuccessful diversity programs or policies, thereby avoiding unnecessary risks to research participants.

To address the need for more comprehensive data and to establish a global baseline measure, in 2019, the Tufts Center for the Study of Drug Development (CSDD)—supported by a research grant from Merck Sharp & Dohme Corp.—conducted a study to address the following objectives:

- Assess the availability and disclosure of participant demographic subgroup data provided by pharmaceutical and biotechnology companies.
- Gather data to inform a baseline assessment of the extent of participant demographic subgroup disparities in the clinical trials of new drug approvals.
- Establish and convey an approach that the FDA, and other stakeholders alike, can apply to improve the value of the Drug Trial Snapshots program and other diversity initiatives.

Since supplemental trials are not required to be reported, this article focuses on disparity in pivotal trial data.

## **Methods**

Tufts CSDD compiled participant demographic subgroup data (i.e., sex, race, ethnicity, age) from pivotal trials supporting all new drugs and biologics approved by the FDA between 2007 and 2017 (n=341). Most of the data were drawn from the FDA website. Tufts CSDD referred to publicly available sources, including ClinicalTrials.gov, medical reviews, and product labeling. Prevalence and incidence data were collected from published sources, including government websites, national health organizations, and peer-reviewed literature.

Tufts CSDD created a summary metric, called the “disparity percentage,” to characterize participant demographic subgroup underrepresentation. This metric is defined as the difference between total actual number of participants by subgroup and the expected level of subgroup representation, divided by the expected level of subgroup participation.

Disease prevalence rates were found in the peer-reviewed literature and public sources for 57% of all approvals. For the remaining 43%, U.S. census data were used as a proxy for the

distribution of participant demographic subgroups, as it was assumed that prevalence was distributed proportionately among the population.

Data on 757 pivotal clinical trials and 592,168 study participants were analyzed. An example of the disparity percentage is shown in Figure 1:

**Figure 1: Calculating a Disparity Percentage**

Disease Condition for Approved Drug:	Peripheral T-Cell Lymphoma
Total Clinical Trial Participants:	788
“Actual” Distribution of Participants Who are Black or of African Descent:	3.7% (29 participants)
Expected or “Predicted” Distribution of Participants Who are Black or of African Descent:	13.5% (106 participants)
<b>Disparity Percentage</b>	<b>-72.6%</b>

## Results/Discussion

### *Data Completeness*

While government guidelines mandate that federally funded clinical research to disclose participant demographic data, race/ethnicity data remain incomplete and underreported. Nearly 20% of all drug and biologic approvals between 2007 and 2017 were missing data on participant race for all referenced pivotal trials. More surprisingly, 50% of drug approvals did not include participant ethnicity data on any of their trials (see Table 1).

The level of drug approval data completeness showed notable increases in participant representation by sex and age at 96.2% and 91.8%, respectively. The availability of demographic data for pivotal clinical trials showed a similar pattern, with higher completion rates for participant sex (89.7%), age (83.2%), and race (72.8%) and a considerably lower level of availability rate for study participant ethnicity (36.7%).

The availability of participant demographic subgroup data for all 757 pivotal clinical trials approved in the 10-year period was substantially low; only 36.7% had data available on participant ethnicity and 72.8% of trials had data on participant race. The dearth of available ethnicity data represents both the need to enroll more minorities in studies and the need to be more intentional in referencing health disparate populations.

**Table 1: Data Transparency in NDAs and BLAs, 2007 to 2017**

	<b>NDAs and BLAs with Data Available on Participants (n=341)</b>	<b>% of Total</b>	<b>Pivotal Trials with Data Available on Participants (n=757)</b>	<b>% of Total</b>
<b>Sex</b>	328	96.2%	679	89.7%
<b>Race</b>	282	82.7%	551	72.8%
<b>Ethnicity</b>	171	50.1%	278	36.7%
<b>Age</b>	313	91.8%	630	83.2%

*Note: Drug data collected from the FDA website. Pivotal trial data collected from the FDA drug information portal for medical reviews and printed labeling for each approved drug.*

*Participant Demographic Subgroup Representation*

The highest overall levels of underrepresentation were observed among participants of Black or of African descent, with nearly 47,000 fewer participants than expected (see Table 2). “Other” participants (e.g., Native American, Native Alaskan, Native Hawai’ian, or Pacific Islander) and Hispanic or LatinX participants were also under-represented, with 11,641 and 4,669 fewer participants than expected, respectively. Roughly 20,000 fewer women were enrolled in pivotal clinical trials than expected levels. Asian participants were over enrolled by more than 23,000 participants in pivotal trials, a disparity of +148.9%.

Overrepresentation among Asian participants may be due, in part, to market access requirements in key geographies including Japan and China.<sup>{5}</sup> However, country-specific variation in the characterization of demographic subgroups may also be a contributing factor. Some studies counted participants of Indian descent as Asian while others did not.

Treating minority populations as homogeneous assumes cultural beliefs and experiences are the same, which could potentially influence racial/ethnic stereotypes about patients and implicit biases in research settings.{6} Understanding cultural differences within subpopulations could amend the cycle of participant distrust in clinical research.

Moreover, inconsistent implementation of racial/ethnic classifications negatively impacts participant disparity percentages. Any significant differences found between groups differentially affects the generalizability of clinical research. Disaggregated analyses may increase our ability to understand exposures and health outcomes across subgroups.{7}

**Table 2: Subgroup Disparities for Pivotal Trials (n=757)**

	Sex		Race and Ethnicity				
	Female	Male	White	Black	Asian	Hispanic/ LatinX	Other
<b>Total participants</b>	252,586	309,844	346,884	24,612	39,244	32,877	13,612
<b>Distribution of total participants</b>	44.9%	55.1%	75.9%	5.4%	8.6%	7.2%	3.0%
<b>Expected level of participation*</b>	272,616	288,137	305,443	71,226	15,764	37,546	25,253
<b>Expected distribution</b>	48.6%	51.4%	67.1%	15.6%	3.5%	8.2%	5.5%
<b>Difference</b>	-20,030	+21,707	+41,441	-46,614	+23,480	-4,669	-11,641
<b>Disparity percentage</b>	-7.3%	+7.5%	+13.6	-65.4%	+148.9%	-12.4%	-46.1%

*\*Based on U.S census and disease prevalence.*

Wide variation was observed in the disparity percentages for participant demographic subgroups by individual disease condition. Pulmonary/respiratory disease, neurology, and rheumatology require the most attention and remediation, with racial and ethnic disparities observed for more than 80% of the total approvals for these indications (see Table 3). While these diseases

disproportionately affect non-white individuals, pivotal trials in these areas had the highest under-representation of Black/African Americans, Hispanic/LatinX and “Other” subgroups.

Black/African American representation in pivotal trials conducted during 2007 through 2017 was considerably low. Based on the analysis of the data available, three times as many Black/African American participants should have been enrolled in clinical trials during the period observed to be adequately represented by disease prevalence rates or by population census figures. Similarly, the Hispanic/LatinX community was highly underrepresented in pivotal trials of investigational oncology treatments. Gastroenterology and rheumatology were the two top therapeutic areas with high levels of Asian participant under-representation.

**Table 3: Top Therapeutic Areas with Participant Demographic Disparities**

<b>Subgroup</b>	<b>Therapeutic Area</b>	<b>Approved Drugs which Underrepresent Demographic (&gt;20%)</b>	<b>Average Disparity Percentage per Drug</b>
Black/African American	Pulmonary/respiratory diseases	100%	-80%
	Rheumatology	100%	-80%
	Neurology	88%	-70%
Asian	Gastroenterology	100%	-86%
	Rheumatology	83%	-46%
Hispanic/LatinX	Oncology	93%	-63%
	Neurology	85%	-54%
	Pulmonary/respiratory diseases	80%	-51%
Other Racial Identities	Neurology	89%	-72%
	Pulmonary/respiratory diseases	86%	-72%
	Immunology	100%	-71%

## **Conclusion**

Findings from the Tufts CSDD study highlight not only the need to improve transparency and reporting of clinical trial participant demographic data, but also the high level of participant subgroup under-representation in FDA-regulated pivotal trials during the past 11 years.

Developing trust between study participants and clinical research professionals begins with improvements in transparency and disclosure. The results of this study indicate efforts to improve participant diversity have not been broadly successful and more needs to be done.

This study has its limitations. The analysis is based on publicly available data. As a result, the findings may underestimate participant subgroup diversity levels. It is likely that sponsor companies collected but did not report participant demographics for some of their trials; further emphasizing the need for disclosure and reporting in the industry.

The results do not include an assessment of drug development programs that failed to receive FDA approval. Additionally, Tufts CSDD relied on U.S. census data to determine the expected or predicted level of population demographic representation when disease-specific prevalence rates were unknown. Future research will look to apply country-specific population census data and other study exclusion criteria to improve the accuracy of diversity assessment.

Low levels of trust, poor access, study participation burden, low education, and lack of clinical trial awareness are among the many barriers that contribute to minority under-representation in clinical research. Poor disclosure and transparency have contributed to public distrust.{8} Improvements in data reporting and completeness on participant demographic diversity will not only go far in improving public trust, they will also play a key role in guiding the clinical research enterprise in addressing the under-representation of participants by race and ethnicity.{9}

## **Authors' Notes**

*Data collection began in 2018 and continued into 2019. While more current data are available now, these were not available at the time our data collection was completed and were out-of-*



scope for the project being conducted. Tufts plans to periodically update the dataset with more current data. In calculating the impact of FDASIA, we see little evidence of change over time for the years leading up to and after 2012, but in time an examination of this topic may make up its own paper.

Kenneth A. Getz reports an educational grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp. during the conduct of the study.

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PEER REVIEWED

## **A Review of the FDA Process, Implementation, and Future Directions for the Approval of Electronic Nicotine Delivery Systems (ENDS)**

Mario Esquivel, MS, ACRP-CP



*Tobacco use in the United States amongst adults has consistently been the leading cause of preventable death.<sup>{1}</sup> Smoking adoption by men and women had steadily increased between 1900 and 1960, but has been on the decline ever since.<sup>{2}</sup> Tobacco control measures had been put in place to curb the use; however, a national policy regarding the oversight of tobacco products was not passed until 2009, with the arrival of the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act). This legislation granted the U.S. Food and Drug Administration (FDA) the ability to regulate tobacco products. In this paper, I will examine the current application process for tobacco products—more specifically, electronic nicotine delivery systems (ENDS).*

### **Background**

Among other things, the Tobacco Control Act imposed new warning label requirements and label standards on tobacco packaging, banned flavored cigarettes, reigned in tobacco advertising to children, and initiated a process for tobacco products to receive approval from the FDA prior to marketing. The impact of the pre-market review process on tobacco products cannot be understated—tobacco products were previously regulated through Congressional regulations that dealt with the sale to minors and distribution licensing of products rather than public health.

Before passage of the Act, Congress had sole authority in the regulation of tobacco products.{3} This was a result of the overturning of the FDA Rule by the Supreme Court in 2000. The FDA Rule was, legislatively, the agency's first attempt to reign in tobacco products and demonstrate that they were under its authority. It was a unilateral decision by the FDA, in order to reduce tobacco use in minors.{4}

The Supreme Court ruling found that Congress had not formally given the FDA authority to regulate tobacco products; thus, oversight was returned to Congress, though the responsibility was not efficiently managed during this time period.{5} The Tobacco Control Act, on the other hand, significantly reigned in the tobacco market and provided safeguards to protect the welfare of general public.

### **The Beginning of ENDS**

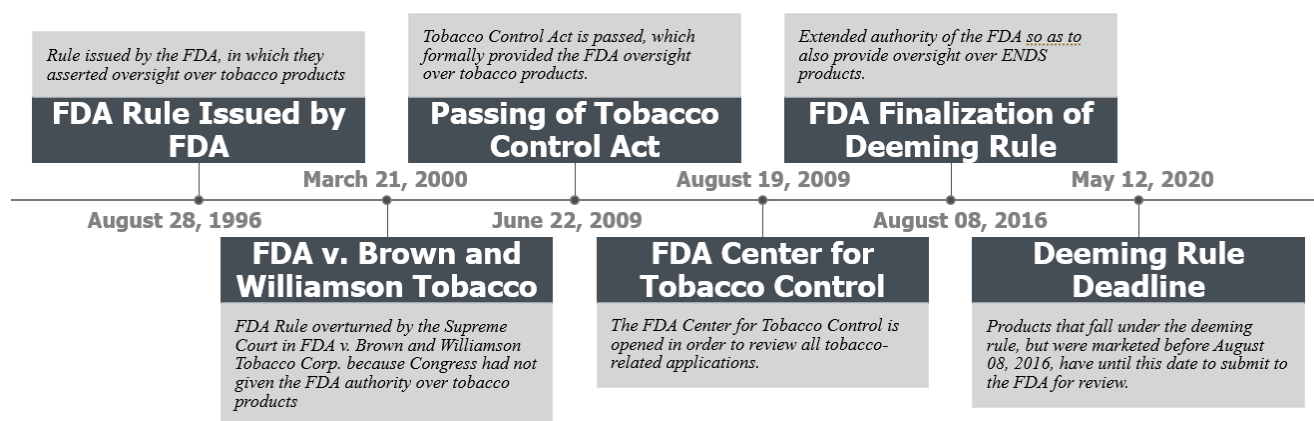
The Tobacco Control Act provided general direction for the regulation of cigarettes but did not go beyond the purview of what was already in the market. Because of this, the market shifted to give rise to the next generation of tobacco products in the form of ENDS devices, also known as e-cigarettes.

ENDS are nicotine products that are generally composed of an electronic heating element along with a liquid nicotine cartridge that is heated to form nicotine vapor for oral absorption.{6} With the passing of the Tobacco Control Act, cigarette regulations had been implemented, but overarching rules for ENDS development and marketing had largely been ignored or were never discussed.

The FDA had to set a standard for providing oversight of ENDS, so in 2016, the agency drafted guidance by which to regulate ENDS products under the Tobacco Control Act.{7} This Deeming Rule, which deemed all tobacco and ENDS products to be under the purview of the FDA, was made in response to the overwhelming increase in ENDS in the market. In summary, the Deeming Rule imposed a stop on independent manufacturing of ENDS and their associated cartridges (see Figure 1 for a timeline of important events related to tobacco legislation).

Additionally, any tobacco product on the market prior to February 15, 2007 would be grandfathered into the market, but products marketed after this date would require FDA approval. There was some leniency—products that were on the market before August 8, 2016 that were not grandfathered in would be subject to the FDA policies and could continue to be marketed, but were required to be submitted for review no later than May 12, 2020. Failure to meet this deadline would result in a product’s removal from the market. A draft guidance was provided to industry but was not finalized until June 2019.

**Figure 1: Timeline of Major Events in Tobacco Regulation History**



### Pre-Market Approval Process Overview

In many respects, the review and approval processes for ENDS devices are very similar to the rules for the FDA medical device regulatory pathways. There are three methods by which new ENDS products can be approved (see Table 1 for summary).

The *Pre-Market Tobacco Application* (PMTA) asks manufacturers to demonstrate that a new product would be “appropriate for the protection of the public health.” The purpose of a PMTA is to provide scientific data that support this endeavor by demonstrating the risks or benefits of the device as a whole, whether people who use or don’t use tobacco products would be more or less likely to use them given the existence of the new product, and the use of appropriate controls and manufacturing processes in making the product.

The *Substantial Equivalence* (SE) pathway is intended for tobacco products that may be found “substantially equivalent” to a predicate product, or if there are some differences, demonstrating that the new product does not raise new concerns for public health versus the predicate.

The *Substantial Equivalence Exemption* (EX) pathway is for tobacco products that have already been approved. These products would have to be modified by adding or deleting a tobacco additive, or by increasing or decreasing the quantity of tobacco featured.

For the purposes of this paper we will only be looking at the PMTA pathway, as most ENDS products will not have already received approval, and as such, will not have a predicate device available which would allow for any SE submission.

**Table 1: Tobacco Product Approval Pathways**

<b>Approval Pathway</b>	<b>Purpose</b>	<b>Products Allowed in Pathway</b>	<b>Time from Submission to FDA Response</b>	<b>Similarity to Device Approval</b>
Pre-Market Tobacco Application (PMTA)	Demonstrate that a new, never approved, tobacco product would be appropriate for the protection of public health	Any new tobacco product marketed after 2/15/2007	180 days	Pre-Market Approval
Substantial Equivalence (SE)	Show equivalence to a predicate product that has already received approval from the FDA	Any product that has received PMTA approval or was marketed before 2/15/2007	90–180 days	510(k) Application
Substantial Equivalence Exemption (EX)	Pathway for products that are modified by adding/deleting tobacco additive or increasing/decreasing quantity of tobacco	Any product that has received PMTA approval or was marketed before 2/15/2007	90 days	Device Class I Exemption

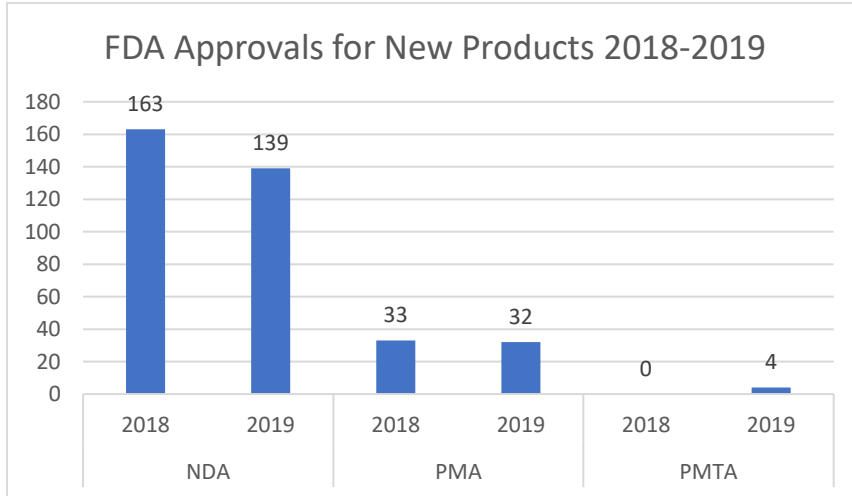
## Methods

Data were obtained from FDA online archives of all PMTA packages from industry and the resulting marketing decisions. PMTA submissions were reviewed and compared to New Drug Applications (NDAs) and Pre-Market Applications (PMAs) over a two-year period (January 2018 through December 2019). Analyses were performed in March 2020.

## Results

ENDS device submissions to the FDA had not really advanced to the PMTA level until fairly recently. Over a two-year period, only four ENDS products were approved by the FDA. In comparison, more than 350 new drugs and devices had been approved in that same timespan. (see Figure 2).

**Figure 2: FDA Approvals for New Products via New Drug Application (NDA), Pre-Market Approval (PMA), and Pre-Market Tobacco Approval (PMTA)**



*Data sources:* [www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals](http://www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals), [www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm), and [www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-PMTA-since-Program-Inception](http://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=ctp&id=%20CTP-OS-total-PMTA-since-Program-Inception).

## **Discussion**

The regulatory approvals for new tobacco products are in its infancy. As stated previously, FDA guidance was finalized as recently as November 2019, and any new products to be marketed after May 2020 require FDA approval. Compared to drugs and devices, the pool of products that will need a PMTA is fairly small.

As seen in Figure 2, only four ENDS products have been approved for marketing through the PMTA process in the U.S. since 2018. In comparison, there are many more approved applications for medical devices and drugs during that same time span. Although there obviously is no equivalency between the three categories, considering that the deadline for review of existing tobacco products was May of this year, there should be a sense of urgency from the tobacco industry to meet the demands of smokers in the U.S. There will be a huge windfall of banned e-cigarettes in the market at this rate, because any unapproved tobacco products will be taken off the shelves.

These regulations have had an impact on the tobacco industry, in that they have effectively relegated innovation within the field of tobacco science to larger companies. Smaller companies will have a much harder time breaking through and competing with larger companies. {8} New tobacco companies will have to be developed more in line with other drug and medical device conglomerates. Cessation of nicotine addiction is a lofty goal; it will only be harder to achieve if the development of potential solutions is stonewalled due to lack of resources.

## **Conclusion and Future Considerations**

It is a great step forward that these products are now regulated under the FDA. The previous system was difficult to manage and varied from state to state. Rather than ensuring the safety of the public, the previous system had only considered interstate trade. The new system in place ensures that all tobacco products are thoroughly reviewed prior to marketing. There are potential concerns with the effect the regulations will have on smaller tobacco companies; however, the protection of the general welfare of the public must come first in the realm of tobacco products.



Innovation begets innovation—the tobacco industry is no exception. As the markets had shifted once already from cigarettes to ENDS, the market is once again shifting—this time from ENDS products to disposable e-cigarettes. These new, disposable nicotine products are not that different from the current ENDS products—the only difference between the two is the intended use.

ENDS products are intended to be used multiple time, with users only having to put in a new cartridge every time they want to vape. In contrast, the new format of disposable nicotine devices offers the same safe route of administration as the ENDS products but is only intended to be used once and disposed of. The current regulations only cover ENDS with refillable cartridges, so exploration of how the regulations affect the newer products is needed.

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## Representation in Clinical Trials: A Review on Reaching Underrepresented Populations in Research

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In a recent report from the U.S. Food and Drug Administration (FDA) on its 2018 Drug Trial Snapshots, there is a significant imbalance in representation of minorities in clinical research. Whites make up 67% of the U.S. population, but are 83% of research participants.[1] Black/African Americans make up 13.4% of the U.S. population, but only 5% of trial participants. Hispanic/Latinos represent 18.1% of the U.S. population, but less than 1% of trial participants.{2}

Further, a recent examination of the topic found that, of the 5,157 patients who participated in oncology trials, 38% were women, 68% were White/European American, 15% were Asian American, 4% were Black/African American, 4% were Hispanic/Latino, 50% were 65 years and older, and only 38% were residing in the U.S.{3} Even with attempts to regulate and include participants from more ethnic backgrounds in studies, 48% of the adult trials did not meet the target recruitment goal for including underrepresented populations (i.e., Black/African Americans, Hispanics/Latinos, Asian Americans, and other populations with different ethnic backgrounds).{4}

Participants in clinical trials should reflect the diversity of the population, with particular attention to those most affected by the disease. A lack of representation from racial/ethnic minority groups in clinical trials has resulted in the development of interventions that have not translated well into real-world use and have not been efficacious in different populations.

For example, 5-Fluorouracil, a commonly used cancer chemotherapeutic drug, has been frequently reported to exhibit differences in drug response among different populations.<sup>{5}</sup> A major side effect associated with this fluoropyrimidine-based drug is the occurrence of hematologic toxicities, including leukopenia and anemia. These toxicities are often found to occur in higher rates in underrepresented populations than White/European Americans. However, the clinical trials conducted to test the drug were overrepresented with White/European American participants; thereby, missing the opportunity to assess the adverse side effects in racial/ethnic minority groups.

Differences in lived experiences, opportunity, and exposure to environmental stressors and toxins among racial/ethnic groups can be missed when clinical trials fail to test interventions on diverse participants. The purpose of this article is to highlight the top five major challenges facing populations who are underrepresented in research, and to identify several strategies to promote diversity in participation.

## **Challenges**

### *Challenge 1: Low Income as a Barrier to Participation*

The first challenge is income. In a prospective survey study conducted in 2016, patients with household annual incomes below \$50,000 were 27% less likely to participate in clinical trials, and as income dropped, so did the likelihood of trial participation.<sup>{6}</sup>

As explained by the FDA, ethnic minority groups are affected more by poverty and lower socioeconomic status and, in turn, this leads to poorer health in their communities.<sup>{7}</sup> Due to lower socioeconomic status, many members of these ethnic minority communities receive hourly wages, which makes it difficult for them to find the time to fit trial participation into their weekly schedule.

### *Challenge 2: Investigator Bias*

The second challenge is bias. Sponsors often have to rely on healthcare professionals to tell their patients about a clinical trial. Unfortunately, healthcare professionals also hold their own biases that sometimes interfere with enrolling racial/ethnic minorities in studies.

For example, healthcare professionals have been shown to withhold treatments based on preconceived notions about whether the racial/ethnic minority patient would adhere to the protocol.{8} Many potential participants never receive information about a possible study due to these biases exacerbating enrollment gaps in studies.

Additionally, racial/ethnic minorities are more likely to trust a provider from a background similar to their own. The race of the physician often influences the racial makeup of the clinical trial volunteers they most successfully inspire toward participation. Given the lack of adequate representation of medical providers and investigators from racial/ethnic minority groups, few minority patients are likely to enroll in clinical trials.{9}

Further, it is an unfortunate trend that minority investigators tend to conduct and initiate fewer clinical trials annually. Minority investigators tend to be younger and have limited clinical research infrastructure and less support than their White colleagues.{9}

### *Challenge 3: Medical Mistrust*

The third challenge is mistrust. In one study, researchers gathered responses from 527 Black/African American patients and 382 White/European American patients regarding their levels of trust in doctors. The study showed that Black patients were less likely to trust their doctor to explain how they would participate in research. They also do not trust that they will not be exposed to unnecessary risks.{7}

These perceptions of mistrust were not totally unfounded. There has been a long history of medical and scientific exploitation that has targeted and adversely affected Black/African American people. The lack of trust between racial/ethnic minorities and their providers is often

associated with a perception that they are asked to take on most of the risks associated with medical research.{7}

Despite these challenges, Black community members have shown more willingness to participate in prevention and wellness studies than drug trials, and there is some evidence showing willingness to participate in studies involving blood draws and other medical procedures.{10}

#### *Challenge 4: Limited Health and Research Literacy*

The fourth challenge is health and research literacy. Many racial/ethnic minority populations have less access to updated information about health conditions and research, thereby limiting their understanding of the symptoms of disease or the clinical research process. Due to lack of

medical and health information, many racial/ethnic minorities may delay seeking treatment from professionals or misunderstand the appropriate circumstances under which it is important to seek treatment. They may also know little about which treatment options are available to them, including clinical research and trials as care options.{7}

#### *Challenge 5: Lack of Access to Transportation*

A fifth challenge is transportation. Many minorities do not live in areas with easily accessible care. This requires them to travel farther than others and makes them less likely to participate in research or seek out care options in general.

### **Strategies**

Despite the challenges we have described, there are multiple strategies available to promote diversity in clinical trial participation.

#### *Strategy 1: Promote Culturally Competent Communication and Transparency*

The most important strategic goal involves addressing mistrust through communication and transparency. Communicating in a way that is culturally relevant to the population being engaged with has been shown to promote trust.

Roman Isler, et al. developed a culturally responsive research literacy curricula that educates community members about the importance of participating in clinical research. {11} Others are making efforts to ensure that research materials (i.e., recruitment materials, informed consent documents, study results, etc.) are designed in ways that promote clear understanding of the research questions, study design, participant protections, and potential community benefit. {12}

Communication should also promote transparency and addressing community concerns. By addressing racial/ethnic minority community members' concerns about the trial early, they are more willing to participate and to trust the provider. It is also key to reiterate the benefits to them of participating in clinical trials and research; these include gaining access to expert medical care, learning more about their condition, and playing an active role in their own personal healthcare. {13}

#### *Strategy 2: Provide Financial Support and Supportive Services to Promote Participation*

To address income-related challenges, it is important to provide adequate participant compensation that also addresses healthcare needs post-participation. Many participants avoid participation because of concerns regarding insurance companies denying coverage for conditions that develop after clinical trial participation. {14} It is important for investigators to consider how adverse side effects would be addressed for participants post-study.

Additionally, investigators could consider providing caregiving support for those who otherwise could not participate due to work or family obligations. Alternative strategies including offering a home visit option for those who might not be able to leave their home and extended office hours for those who have work conflicts.

When longer site hours and home visits are options, they allow for the participant to come to the trial site at a convenient time after work or can lift the burden of finding and paying a sitter. Home visits are the best options for many geographically isolated patients to not have an added burden of finding transportation to and from the trial location.

### Strategy 3: Provide Transportation Support

To address transportation challenges related to geographic isolation from healthcare resources, researchers can provide transportation, subsidize gas and parking fees, or provide options for telemedicine using mobile technology. Telemedicine and mobile technology allow the patient to remotely connect with their provider and not have to take a large amount of time out of their day to receive care and/or participate in a trial. { 1 } Providing transportation assistance allows the participant to reach the trial site more easily and to worry less about the cost and impact on their schedule.

### Conclusion

By building a bridge between research and participants, we can reach more racial/ethnic groups and provide better health interventions to those who need it the most.

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#### **Authors' Note**

At Javara, we recognize the importance of building the next generation of clinical research professionals and are committed to fostering growth in our interns by providing hands-on experiences. There is a need for organizations to create opportunities for the clinical research professionals of the future—in the U.S. alone, there are more than 44,000 jobs related to clinical research available.

Javara is deeply committed to the advancement of clinical research with workforce innovation aimed at growing the future leaders of our industry and promoting clinical trial awareness, education, and training through our summer internship programs. We also provide our students with the tools and experiences needed to promote clinical research as a care option by offering corporate and clinical internships with opportunities spanning the realms of study start-up, trial activation, patient engagement, recruitment, communications, legal issues, direct patient care, and more.



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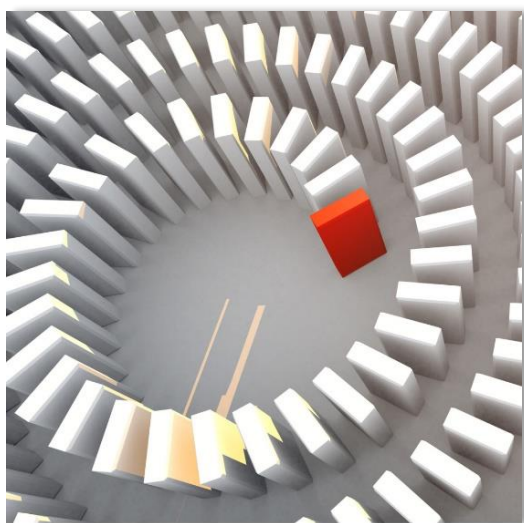


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SPECIAL FEATURE

## The Impact of COVID-19 on Clinical Trial Activities and the Research Environment

Achenyo Ochuma, MSc



*The emergence of the COVID-19 pandemic has resulted in a significant impact globally across various sectors and industries leading to a rapid shift in adapting processes and systems. The nature of COVID-19 is an infectious disease characterised as a respiratory illness associated to other severe symptoms affecting individuals in varying degrees. Following a [statement by the World Health Organization \(WHO\)](#) on January 30, 2020 declaring the outbreak as a Public Health Emergency of*

*International Concern, it has become an ongoing global health priority. Undoubtedly, this directly has an impact on the pharmaceutical and healthcare industries. This article provides an overview of this crisis from the perspective of how clinical trials and activities in the research environment are being managed.*

### Background

Around the world, various organizations, authorities, and agencies are assessing the impact and providing guidance to enable management of clinical trials and research in the midst of the unprecedented healthcare situation presented by COVID-19. The key authorities include the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA), the European Medicines Agency (EMA), and U.S. Food and Drug Administration (FDA).

Considerations have been taken for ongoing clinical trials around existing policies and procedures that have to be modified. The overall impact on sponsors, contract research organizations (CROs), sites, and participants depend on several factors and the status of trials. Steps which are critical to determining the impact involve processes covering risk assessments, action plans, and revised agreements between the parties involved.

The global crisis has highlighted the importance of a collective effort in the management of clinical trials. As covered in the following sections, this requires looking at the challenges from the perspective of various aspects of the clinical research landscape, ranging from operational to regulatory issues.

## **Sponsors**

The results from a recent analysis conducted by [Medidata](#) show how ongoing research has been affected globally by the pandemic in terms of active studies at sites. A significant decline in the entry of new patients into studies in active recruitment was noted, starting in China in February 2020. Similar trends were noticed across the U.S. and European Union (EU) starting around March 2020. {1}

It is crucial for sponsors to have detailed reporting and analytics in real time in order to adequately assess the impact on trials at a patient, site, and country level to effectively mitigate risks. In April 2020, several large pharmaceutical and smaller biotech companies announced modification of their research and development plans in the form of either temporary delay in site activation or patient recruitment in some trials. {2}

Broadly speaking the challenges being addressed by sponsors cover a combination of:

- Overall oversight on trials status, timelines, and risk management
- Action plans for evaluating continuation of studies
- Protocol deviations
- Safety of participants
- Data quality
- Supply, distribution, and logistics of investigational medicinal products
- Monitoring and audits

## Sites and CROs

In response to the pandemic, the [Association of Clinical Research Organizations \(ACRO\)](#) released recommendations for oversight and monitoring of trials that cover the activities of sites, sponsors, and other organizations. The aims are for interim emergency measures to be in place during the ongoing health crisis period. The overview consists of considerations for general oversight, interim measures documentation; routine monitoring resumption, and database lock.{3}

From the perspective of sites, impacts relating to the above considerations will be determined by a decline in the recruitment or screening process leading to delayed start-up of studies or ultimately halted studies. Changes to how site visits by patients are handled therefore are necessitating utilization of remote access tools in many cases. Modification of study models will enhance capability for specific diagnostic testing required for each study. This implies an additional administrative burden in order to accommodate these and other changes.

For ongoing studies, the issue of informed consent must be addressed in terms of how it will be captured, based on the format of informed consent forms. Meanwhile, monitoring the storage conditions of the investigational medicinal product (IMP) is essential, and is just one aspect of monitoring research subjects' safety and the efficacy and credibility of data during a trial. The severity of the impacts on each study will vary depending on the phase of the trial.

On a broader level, the role of CROs in managing the impact depends on proactive decisions made through cross functional working at all levels to control resources internally. Partnerships with vendors externally form part of the dialogue in order to ensure that all areas are efficiently managed, including supply chain and logistics.

The establishment of expert committees or task forces within organizations to focus on implementing action plans for addressing this health crisis and others like it will streamline the necessary activities, and may involve upskilling or repurposing members' expertise to meet the new demands. The review of objectives, milestones, and goals will be incorporated as a result. In

maintaining modified processes, a focus on patient safety as well as on the safety of study teams is essential.

Remote site support services, electronic reporting systems, safety monitoring, and laboratory testing are other areas that also need to be included in the decision-making process.

### **Supply Chain and Logistics**

We can expect a knock on effect and long-term impact from the pandemic on supply chains from manufacturing to distribution, which includes active pharmaceutical ingredients (APIs) and IMPs. Clinical trials have been disrupted due to implications from additional measures such as lockdown, quarantine, and social distancing implemented across the world. Transportation limitations which have arisen increase the demand on other delivery services. The potential issues spinning off from these trends require frequent evaluation as the situation evolves. It is significant to note that regulatory requirements related to these challenges vary in different countries, but are time consuming in any event, and that regulators are setting in place support systems to enhance the stability of the supply chain.

### **Adaptation of Trials**

An article published in the [Drug Information Association \(DIA\) Global Forum in May 2020](#) examines recent dramatic changes in clinical trial operations as the adoption of virtual trials accelerates. This model is based on decentralised trials, whereby patient safety and data quality are maintained, and the platform is run from a mobile device coordinating all study-related procedures to be accessed by eligible participants. The technology allows the network of doctors, nurses, researchers, and data managers to be combined with the platform.

The adoption of such trials has been gradual in the past five years, and the pandemic has created an opportunity where this model could be embraced as the clinical trial landscape changes. The [FDA](#) and [EMA](#) have published guidance on the use of virtual visits to ensure the continuity of trials. {4}

## Regulatory Guidance

The World Health Organization (WHO) has developed a [database](#) of literature for [technical guidance](#) and [global research](#) regarding the coronavirus. WHO has an important role in setting priorities for research and for coordinating and facilitating trials. A recent article in *The Lancet* on the global coalition highlights the launch of the SOLIDARITY trial studying potential treatments for COVID-19 by reviewing the evidence used to generate COVID-19 study guidelines.{5}

Regulatory agencies have issued various guidance documents with regular updates, as outlined below, to enable sponsors and sites to manage the conduct of clinical trials during the pandemic:

- [UK MHRA](#) developed a guidance to support disrupted clinical trials, including ongoing, resumed, and new studies. The guidance highlights flexibility of requirements for these trials, ensuring that the priority should be the safety of participants. Alongside this, the National Institute for Health Research (NIHR) set out a [framework](#) in May 2020 to restart paused research activities.{6} [The Health Research Authority](#) in the UK also provided [guidance](#) for amendments made to existing studies for research conducted by the National Health Service, covering a range of scenarios with oversight to protect participants.
- [FDA](#) guidance provides general considerations to assist sponsors based on ongoing trials, existing policies, and trials impacted by the public health emergency. A question and answer section is featured to address a range of related issues.{7}
- [EMA](#) guidance aims to assist implementation of protocol deviations with advice specific to new trials initiated for potential COVID-19 treatments, according to trial methodology suggestions issued by [EMA's Human Medicines Committee](#).{8}

The lessons derived from the impact of COVID-19 on research activities show that collaboration between pharmaceutical companies, healthcare industries, CROs, patient associations, and regulatory authorities is vital for data integrity and quality of research to be maintained. There are various recommendations to address the considerations taken into account for the broader perspective of the clinical trials landscape. Identifying best practices for trials based on regulatory guidance will shape the future of what research would look like.

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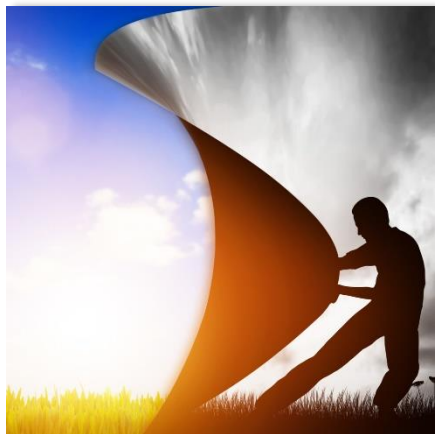
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QUALITY CONCERNS

## **Risk-Based Clinical Trial Management: Harnessing the Transformation of RBM to RBQM**

Patrick Hughes



*Risk-based quality management (RBQM) is a system for managing quality throughout a clinical trial. The data-driven elements of this type of strategy have evolved substantially over the past few years, as an extension to the original principles that underpin risk-based monitoring (RBM). This article will outline the difference between RBM and RBQM, highlighting some of the advantages and benefits of managing all areas of quality in a clinical trial.*

*It will also provide a discussion of the implementation of the method alongside some of the challenges related to embracing the change. It will outline how sponsors and contract research organizations (CROs) can harness the power of risk-based trial management, making clinical trials better, faster, and cheaper for the industry and safer for patients.*

### **A Need for Change**

From the year 2000, a continual increase in the complexity of clinical trial designs, highly publicized safety issues with marketed drugs, and a slowing of innovation coupled with patent expirations saw the cost and duration of clinical development steadily increase, while profit margins dwindled. While the previous decade had been a time of relative economic health for the biopharmaceutical industry, at the turn of the century drug makers found themselves faced with growing pressure from multiple directions.

Between 2000 and 2012, a review of marketing submissions to the U.S. Food and Drug Administration revealed that about one-third (32%) of all first-cycle review failures, or 16% of submissions overall, were driven by quality issues.<sup>{ 1 }</sup> The increasing complexity of trials means they take longer and cost more. This dynamic also adds significant risk to the operational success of research, both in terms of recruiting and retaining patients, and in generating the reliable results needed to support ultimate marketing approvals. It is apparent that the traditional way of conducting trials is not fit for the 21st century.

## **Understanding RBM**

RBM, which is most efficiently achieved by sponsors harnessing technology and real-time information to proactively monitor risk, was written into U.S. and European regulatory guidance in 2013. In its simplest form, RBM strategies use software, data inputs, and analytics to monitor risk and support critical thinking and decision making. By giving sponsors the ability to identify and correct issues as and when they arise, RBM can improve data quality and patient safety as well as reduce costs.

At its core, RBM is the operational analogue to the tenets of “quality by design” (QbD). Both models have the same fundamental goal of improving the operational success rate of clinical research through higher quality, shorter timelines, and greater efficiency. QbD and RBM are also linked by methodology, as they both call for ongoing assessment and mitigation of operational risk.

## **Embracing RBQM**

RBQM methodology is a very timely development that sponsors and CROs are now embracing to address the growing crisis in research complexity, duration, and cost. The latest version of the Good Clinical Practice (GCP) quality standard extends the RBM approach to every aspect of study execution, applying the principles to all areas of quality management. The ICH E6(R2) guideline for GCP from the International Council for Harmonization outlines the driving factors of this approach, including the transition away from largely paper-based research to the modern approach of electronic and digital technologies including electronic data capture, electronic

clinical outcome assessment, and interactive response technology. This has opened a tremendous opportunity to plan and manage clinical research more effectively and efficiently.

RBQM implementation can be overwhelming for an organization, given the wealth of information that is currently available. Starting simple is the way to maintain focus and concentrate on the elements of RBQM that are most important to gain immediate quick wins and success in the long term. The key to success is to apply thoughtful but simple processes, smart technology, and a focus on evolutionary change management.

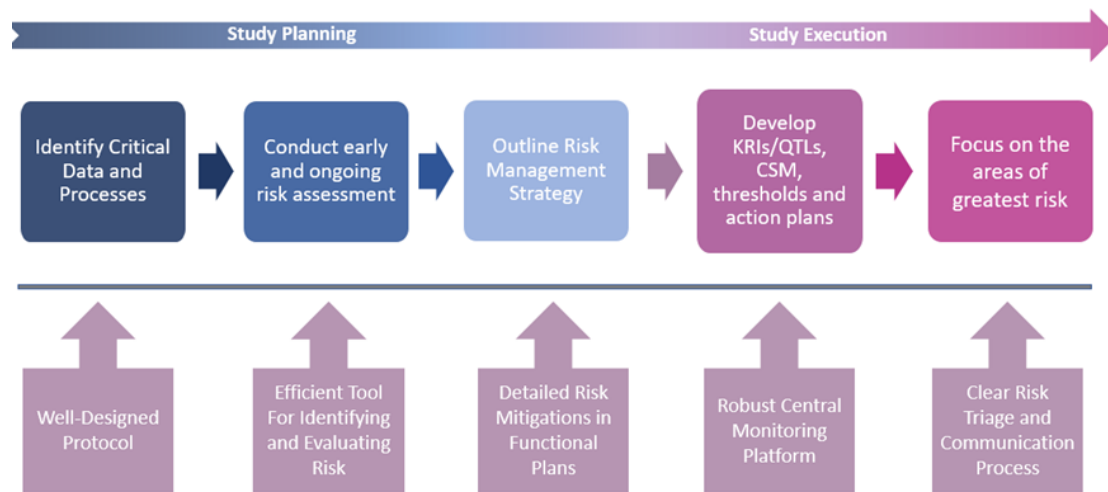
### **Making the Transition**

RBQM encompasses all elements of the study, from planning right through to execution. Risk management underpins the overall quality of the trial by identifying, controlling, and communicating. ICH E6(R2) sets out what a gold standard RBQM system should cover:

- Critical process and data identification
- Risk identifications
- Risk evaluation
- Risk control
- Risk communication
- Risk review
- Risk reporting

Further, centralized statistical monitoring (CSM) is a critical component of the operational success of RBQM, as it is a key and under-used weapon for quality oversight. CSM lies at the heart of RBQM (see Figure 1). It interrogates all clinical and key operational data to find anomalies and discrepancies that would remain undetected by traditional techniques. It is more than just computing statistics on a subset of key variables—it is about processing all data and guiding users to where the potential issues might lie, or a “boil the ocean” approach to risk identification and mitigation.

**Figure 1: Centralized Statistical Monitoring Model**



An effective centralized monitoring approach should include the following three components:

- Data surveillance
- Key risk indicators (KRIs)
- Quality tolerance limits (QTLs)

When it comes to KRIs and QTLs, quality is much more important than quantity. Sponsors and CROs should identify a core set (10 to 15) of appropriate KRIs and focus on ensuring that these are optimized to detect risk as early as possible and minimize likelihood of false alerting.

The same principle should apply to QTLs (four or five), which should focus on the most important study-level risks, or “failure points.” Data surveillance, which is sometimes referred to as CSM, has been under-appreciated and under-utilized by many organizations, but provides an effective independent and objective quality oversight process.

While KRIs and QTLs are designed to monitor for pre-identified areas of risk, data surveillance or CSM can expose forms of study abnormality and misconduct that may be difficult to identify and/or characterize during pre-study risk planning. By running a comprehensive set of well-designed statistical tests across a broad swath of study data, the method can spot atypical patterns that represent potential intentional or non-intentional misconduct. It can flag issues such as fraud, sloppiness, or training needs, as well as malfunctioning or poorly calibrated study equipment.

## **Elements to Success**

RBQM relies on a combination of different tools. A central monitoring platform can act as the enabling technology, encompassing central data review, risk assessment, KRIs, data quality oversight, and issue and action tracking management modules. None of the key components of RBQM implementation, including pre-study risk planning, adaptive/dynamic site monitoring with a significant reduction in source data verification, and centralized monitoring, need to be complex to be effective. Risk findings should be documented thoroughly and accurately for regulatory inspection purposes. A plan should ideally cover the overall objectives, proactive data monitoring, and communication.

The first step in proactive data monitoring is to identify what is possible to mitigate, eliminate, and accept. This all forms part of various plans, including those for data, training, monitoring, statistical analysis, safety, medical monitoring, quality, and other functional plans. KRIs, QTLs, CSM, and risk communication are all crucial to the process to identify risk signals and comply with the regulatory obligations. The entire study team should be aware of the risks and how they are being managed.

Although the many layers of the model may seem daunting at first, sustainable success in adopting RBQM begins with establishing and confirming the primary objectives for adopting the strategy (i.e., what is the organization trying to achieve with RBQM?).

Each of the following three dimensions of value should be considered:

- Improved quality
- Reduced operational costs
- Shorter timelines

## **Moving Forward**

Improving data quality and patient safety, while controlling the spiralling costs of drug development research, were the primary objectives behind the shift toward RBM over the last eight years. The model's success, combined with advances in clinical trial technology, has seen

the approach extended to cover the whole of trial execution in a methodology widely referred to as RBQM. Elements of RBQM can be implemented individually and independently to great success, making clinical trials better, faster, and cheaper for sponsors and CROs and safer for patients.

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## The Centricity of Decentralizing Risk-Based Clinical Trials

Alison Holland



*The ancient Greek philosopher Plato was light-years ahead of his time when he said: “Necessity is the mother of invention.” Hundreds of years later, this maxim still applies, as the COVID-19 pandemic is driving extraordinary inventiveness, including in terms of how researchers are conducting virtual or decentralized clinical trials (DCTs).*

### Background

DCTs are not a brand new idea. For more than a decade, the drug and medical device development industry has been trying to answer the question: How do we bring the study to the patient? DCTs offered a potential answer, yet companies had been wary to adopt this previously relatively untried model. Now, bringing trials to patients is no longer a nice-to-have, as more than half of the top 50 pharmaceutical companies have had to make protocol changes in their ongoing trials since the pandemic began and others have paused trials completely. As of May 20, one-third of sponsors were switching to virtual or decentralized models, according to the Tufts Center for the Study of Drug Development (CSDD).{1}

#### How Do Decentralized Clinical Trials (DCTs) Work?

DCTs leverage technology to treat study patients remotely and through hybrid models that often include minimal in-person visits. Inclusion of digital technologies varies by study, but can include eConsent, telemedicine, wearable devices, electronic clinical outcome assessments (eCOAs), and electronic health (eHealth) records, to name a few. Mobile technologies are often used as electronic diaries and to collect data from wearable sensor devices. Home health nursing or devices shipped to patients allow the performance of assessments such as blood pressure, ECG, and phlebotomy services within the patient’s home. This model improves patient centricity by reducing the burden on study participants while leveraging technology to enable quality doctor/patient interactions.

Part of the industry’s reluctance to adopt DCTs was due to the unknowns around how to safely care for patients and reliably collect data remotely. Further, with regulators’ increased requirements for a risk-based approach to trial management, conservative life sciences companies were barely dipping their toes in the water, limiting experience to small pilot projects.

Fortunately, organizations are establishing new DCT best practices for safety and reliability, and reviewing their internal standard operating procedures and processes to fit into the DCT study design. Additionally, cloud-based platforms are emerging to create a superhighway for patient study data—aggregating all sources, from wearable devices to local lab visits, in real time—enabling real-world evidence strategies to be followed.

Partnerships between technology providers, sites, and labs, too, enable a seamless path to partially or fully DCTs that put patients first and follow a risk-based approach. Now, once-timid biotechs are jumping fully into the DCT ocean and seeing the benefits—more accurate data, increased patient recruitment, better patient engagement, and faster trial execution, to name just a few.

It’s unlikely that companies will ever revert to traditional models. By 2022, nearly two-thirds of active physicians are expected to start using telemedicine.<sup>{2}</sup> Aiding in the adoption are new safety guidelines from the U.S. Food and Drug Administration (FDA);<sup>{3}</sup> meanwhile, the Centers for Medicare and Medicaid Services relaxed its reimbursement rates for telemedicine visits, according to the Trump Administration.<sup>{4}</sup>

Long after the pandemic subsides, companies will recall these dark days and want to be prepared to minimize the risk of trials being disrupted again. Five key steps will help them successfully decentralize in-flight trials and start new DCTs within a risk-based framework.

### **Five Steps to Guide Successful Risk-Based DCTs**

1. Document a specific decentralized study design and implementation plan, including all patient safety, data integrity, and regulatory considerations (see Figure 1).
2. Determine the wearables and devices that are needed, what tools are already being used in the study ecosystem (i.e., interactive response technology, electronic data capture,



central labs, etc.), and other types of support that would be needed (i.e., home health nursing, local labs, etc.).

3. Evaluate how decentralized data will be reviewed and monitored to ensure quality and integrity. For example, define which data are collected for remote patient safety oversight monitoring and which for study endpoint analysis.
4. Equip all sites for success in a decentralized model, considering how it will impact efficiency and daily operations. Map out the options that would be best for each site, including those that are available within a site’s infrastructure already, to leverage different technologies or remote support teams. Additionally, consider what support and training will be needed to enable the sites to engage effectively in DCTs.
5. Enhance the patient/physician relationship in a virtual world by providing options such that study teams, investigators, and patients have choices about how they can participate in a study. It’s important to recognize that one size does not fit all, so flexibility is crucial to allow for physician and patient choice in order for DCTs to be efficient and effective for both parties.

**Figure 1: Patient Safety, Data Integrity, and Regulatory Considerations for DCTs**



**Patient Safety: The North Star for Assessing Risk**

Every study has a risk management plan, but regulations now require evidence that it is being followed, adjusted, and evolving with the study. Patient safety is the north star of risk assessment

for every trial, and especially for DCTs. Eighty-eight percent of clinical trial sponsors surveyed by Medable report that patient safety is paramount when considering a DCT.<sup>{5}</sup> For example, during the COVID-19 health crisis, the first risk-assessment question to determine the feasibility of a DCT has become *“is it safer to continue dosing patients remotely or safer to stop dosing altogether?”* If continued dosing is the safer option, the risk assessment for a DCT continues.

Transitioning in-flight studies to a decentralized model overnight presents the most complicated case for ongoing, safe conduct of a trial. Study leaders need to consider whether safe dosing requires other health checks, such as blood pressure monitoring and vital signs. Then, they need to decide how to accurately measure these factors digitally and/or remotely.

The answer to each question triggers a new set of questions, such as how do you deploy digital measurement devices? How will you train patients or caregivers to use them correctly? Are they available to everyone in the study? How long until you can get the device? A week versus a month or a year? Answers to these questions and more assure patient safety when switching to a DCT.

The second major focus for risk assessment is data integrity. Again, risk factors must be addressed, including patient privacy, accurate data capture, real-time data flow, and reliable reporting. Also to be considered are broader issues regarding data comparability to previously collected data and the impact of data analysis plans on the study.

### **Transformative Value for Sites, Sponsors, and Patients**

There are many advantages to DCTs—even beyond solving many of the problems of recent, pandemic-driven stay-at-home mandates. For example, a DCT model can significantly reduce time spent documenting outcomes, collecting data, and transitioning patients through in-person visits. This opens more time for investigator staff to spend more quality time with patients.

DCTs also extend access to trials for patients who have travel restrictions, can't manage an onsite visit schedule/frequency, or are geographically distant. In fact, 93% of surveyed physicians using telehealth say it improves access.<sup>{2}</sup> “Using digital technologies to bring

clinical trials to the patient, rather than always requiring the patient to travel to the investigator, is an FDA priority,” said former FDA Commissioner Scott Gottlieb, MD, in [March 2019](#).

Overall, DCTs significantly improve trial efficiency and execution—a top priority for sponsors and contract research organizations. From increasing participant diversity and speeding patient enrollment to improving data quality and increasing patient retention, DCTs can trim the fat from slow-moving trials that benefit sites, sponsors, and especially patients.

### **Increased Site Capacity for Additional Studies**

The total number of endpoints in a single clinical trial rose 86% from 2008 to 2018, according to the Tufts CSDD, making the burden on sites almost unbearable.<sup>{6}</sup> Digitizing study processes with tools such as eCOA, electronic/remote informed consent, and electronic patient-reported outcomes allow patients to complete study tasks at home that would typically be performed at the site and frees investigator staff from redundant data entry.

### **Expanded Trial Access and Diversity of Participants**

Distance, travel, and participant diversity have long been challenges in recruitment and in developing therapeutics that are generalizable to the population. DCTs allow patients to participate in clinical research from where they are, removing the barriers of travel and geography to accelerate enrollment, increase retention, and add diversity.

The National Center for Biotechnology Information (NCBI) found that a decentralized model recruited three times as many patients as the traditional model and did so three times faster.<sup>{7}</sup> The patients in the decentralized model also better represented urban and rural areas, whereas the traditional model only consisted of those living near an existing clinical trial site.

These benefits apply to trials across all disease states, but are particularly important for rare diseases, as trials for these are few and far between and participants may be spread across wide geographic areas. Patients are often willing to travel for an initial assessment and final visit—the bookends of their trial experience—but need to maintain their day-to-day life without the burden of frequent site visits, which is only possible in a decentralized model.

## **Improved Data Robustness and Accuracy**

The apps, wearables, and other technologies deployed in DCTs directly track study compliance and patient symptoms, providing more oversight of adherence and enhanced patient safety monitoring. These tools automatically collect data continuously for greater accuracy because they are not reliant on patients to remember or even document many aspects of their study experiences. This also means DCTs can deliver data from the source, eliminating second-hand data sources and reducing the need for transcription verification.

DCTs can also provide insights about how the interventions affect patients' daily lives (real-world evidence). For example, perhaps a medication is suspected of causing an immediate but short-term side effect. If the patient is able to self-administer during his or her regular daily activity, a wearable can record a change in heart rate, respiration, and other data points, providing a physician with real-time visibility of the symptoms rather than waiting for the patient to report them at the next scheduled visit.

If needed, an ad hoc televisit with the patient can be used to record and/or rule out an adverse event and reassure the patient, thus helping prevent a dropout while contributing real-time, real-world evidence to the study.

## **Improved Patient Engagement and Retention**

DCTs decrease participant burden (e.g., travel costs, time off work or away from family), which makes study participation more attractive to patients and caregivers. Fewer visits are especially important for patients with limited mobility, who are working full-time, who are caregivers, or who juggling the time demands of a young family. Investigators strive to support patient recruitment, however sometimes the study burden is off-putting to patients. Further, since two-thirds of investigator sites fail to meet patient enrollment requirements, it is particularly important to take advantage of methods proven to accelerate trial attractiveness and execution.

Bringing the trial to the patient not only accelerates study recruitment times, it minimizes dropouts. The NCBI study mentioned previously showed the trial retention rates were 89% for the decentralized model and only 60% for the traditional model.<sup>{7}</sup> Enhanced retention is driven, too, by the constant “at a click” connection that patients have with their doctor and staff. DCTs offer choices and facilitate connections that provide patients with assurances and physicians with confidence that the patient is safe.

### **Expedited Patient Identification and Cost Reduction**

Patient identification and outreach have always been significant drivers of the costs and inefficiencies of research. In a recent longitudinal study targeting a rare genetic variant of dry age-related macular degeneration, more than 8,000 participants needed to be identified, pre-consented, and screened. Traditional methods would have limited the pool to those living near specific sites and required patients to travel, making it difficult to recruit an adequate number of qualified patients in a reasonable timeframe.

However, leveraging DCT technology, patients were pre-screened at home, enabling the sponsor to reach underrepresented populations, speeding patient enrollment, and improving participant data capture. The decentralized approach reduced the patient enrolment cycle time and costs by \$20 million.<sup>{5}</sup>

### **DCTs are Proving Themselves as a Successful Invention That’s Here to Stay**

From the largest to the emerging, life sciences companies are embracing DCTs, and so are their partners and patients. A recent Site Landscape Survey by the Society for Clinical Research Sites revealed that more than half of sites reported they would do “whatever is required” to conduct a virtual or decentralized trial, while 75% of patients say that collecting all study data from their own home is appealing.<sup>{8}</sup>

Clinical research, wherever it occurs, will always require the expertise and experience of qualified teams that embrace a risk-based approach. By implementing a “patient first” DCT, organizations can shatter the traditional study paradigm and finally achieve sought-after

improvements in patient accessibility, unification of data, and data availability, culminating in faster, more effective trials.

We have the ability to engage with our patients, learn about their lives and priorities, and apply these insights to optimize the study design and mitigate upfront risks. For example, by employing technology to conduct pre-recruitment assessment data collection, companies can understand how people live so that protocols can be customized—bringing a patient-focused experience to clinical research.

While the COVID-19 pandemic has been a catalyst in forcing new clinical trial execution models to go mainstream, they will be part of a mix of options in the long term. The advantages are powerful and the results are the proof—DCTs are here to stay.

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DATA-TECH CONNECT

## **What COVID-19 Teaches Us About Conducting Clinical Research Remotely and Electronically**

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*With the onset of the COVID-19 pandemic, there has been a significant push for research teams to do work remotely. That translates to working electronically while still attempting to accomplish workflows that otherwise would be done face-to-face. This is no easy feat for sites not equipped or prepared for this transition.*

### **Obtaining Informed Consent**

The heart of clinical research is direct patient interaction, and it is during this time that perhaps the most important function researchers must do is obtain consent. With the transition to telework due to COVID-19, researchers were scrambling to re-consent or obtain initial consent without having the patient in the same room. Another related scenario has been consenting patients in isolation due to possible or confirmed COVID-19 infection. What is the best way to capitalize on technology and continue the forward progress of clinical research?



Transitioning a workflow from a traditional paper-based process to an electronic process becomes challenging while maintaining compliance with 21 CFR Part 11 of the *Code of Federal Regulations*. If the research is regulated by the U.S. Food and Drug Administration (FDA), the consent process is a necessary consideration, but if it is not an FDA-regulated study, it becomes less important. FDA forms and documents requiring signatures need them in either scanned or digital format.<sup>{1}</sup> Specific enforceable provisions related to 21 CFR Part 11 include, but are not limited to:

- System access only by authorized persons
- Operational, authority, and device checks
- Education, training, and experience of those who are assigned to develop, maintain, and use these systems
- Documentation controls
- Requirements related to electronic signatures<sup>{2}</sup>

Electronic tools such as DocuSign®, REDCap®, and electronic health records all have the capability to meet 21 CFR Part 11 compliance for electronic consent (eConsent). For example, DocuSign’s Part 11 module was created to be incorporated as part of an “open system” as defined in Section 11.3(b)(9), in which there is electronic communication among multiple people with system access extending to those who are not part of the organization that operates the system.<sup>{3}</sup>

Despite these add-on abilities for compliance, not every organization makes an investment in this type of technology. The absence of these features may leave researchers scrambling for solutions.

Electronic consent can be further complicated by the idea of remote consent. These two very different concepts can be a source of confusion for research study staff. Remote consent occurs when a research participant and the study team member obtaining consent are not in the same location during the consent discussion and form completion. This differs from eConsent, which includes electronic presentation of the information contained in the consent form and an

electronic signature with a date and time stamp placed by the electronic system. eConsent could occur in person or through a remote consent process.

For a study regulated by the FDA, the study team should ensure it utilizes a Part 11-compliant electronic signature system that includes authentication of the research participant's identification, as the signing of the informed consent form cannot be witnessed in person. It is recommended, and often requested from sponsors, for sites to have a standard operating procedure on electronic consent.

In response to the challenges investigators are facing in obtaining informed consent for patients under isolation precautions and those unable to travel to outpatient clinics, the FDA announced that its MyStudies app was being made available for free to investigators.<sup>{4}</sup> The MyStudies app provides a Part 11-compliant means for obtaining informed consent securely from patients interested in clinical research when face-to-face contact is not possible or advised due to COVID-19 restrictions.

### **Conducting Virtual Visits**

Consenting is just one aspect of the research study visit. What about all the other study procedures that need to take place for data collection? While telehealth has been expanding for healthcare organizations in a standard of care capacity, it has seen slow adoption within clinical research. However, virtual study visits can serve as a means of collecting some patient safety and efficacy data while still complying with COVID-19 restrictions.

Virtual visits take full advantage of technology using online platforms to conduct clinical research from the comfort and safety of a patient's home. This could include everything from recruitment and informed consent, to measuring patient endpoints and assessing adverse events.<sup>{5}</sup>

As the pandemic has progressed, it is apparent that patients are in favor of research opportunities that allow them flexible study participation in a convenient way, including 61% in favor of telehealth services.<sup>{6}</sup> Technology that captures behavior and physiologic measures has been on the rise for clinical research since the turn of the century, with a 34% increase in product usage

from 2000 to 2017.<sup>{7}</sup> Capitalizing on these tools can further facilitate the transition to virtual studies.

It is recommended that study sites now making the transition to virtual visits should over-communicate with their patients who are on studies to mitigate concerns related to safety, equipment availability, logistics, and any other related stressors from COVID-19 and the patient's condition.<sup>{8}</sup> Keep in mind that, while virtual visits allow for safe participant assessment and data collection, there are still some shortcomings to this method; clinical laboratory measures, imaging, and other study procedures simply cannot be completed in a remote fashion.

For example, research participants who are unable to come in for onsite laboratory testing may need to use local facilities for safety labs. In such cases, investigators should consider guidance from sponsors (if applicable), institutional review boards (IRBs), as well as site policies and procedures to determine which "in-person" visits are essential to the safety of the research subject, despite the potential risks of conducting in-person study activities during the COVID-19 pandemic.

### **Regulatory Maintenance and IRB Review Considerations**

As site procedures change dramatically from the pandemic, communication with IRBs becomes essential. Most studies will likely need some changes in response to COVID-19 restrictions; this could lead to overwhelmed IRBs if all protocol changes require review and approval. If remote study operations are temporary and do not pose significant risk to the patient, it may be that these operational changes do not need IRB review.

While virtual communications do pose some risks in terms of confidentiality breaches, those risks weighed against the possibility of a COVID-19 infection are minimal. By reducing the number of protocol changes requiring IRB review in response to COVID-19 restrictions, IRBs could avoid being overwhelmed by the volume of submissions.

Investigative sites conducting COVID-19 research need to work quickly through study start-up processes in order to offer investigational COVID-19 treatments to their patients. In support of

this, the FDA issued guidance in June 2020 providing key considerations and recommendations to allow for shorter review timelines for IRBs reviewing submissions for patient access to investigational drugs for treating COVID-19 infections.{9}

The maintenance of essential documents is also impacted by teleworking. Getting signatures on essential documents, such as delegation logs and financial disclosure forms, is challenging remotely, where we once again revisit the best way to obtain electronic signatures. For fillable FDA forms, the FDA prefers that Adobe Sign be used.{1}

## **Training**

Transitioning to remote working and virtual study operations can be challenging for research staff. It is important to provide them with the support, training, and tools they need to continue to operate effectively. For example, research sites within larger organizations may need to investigate applicable institutional policies, such as for data management, that staff should be aware of while conducting research remotely.

An additional consideration is onboarding new hires during the pandemic. Providing newly hired staff with the training they need to be independent, both during and after the pandemic, is a challenge in a remote work setting. However, providing effective training to new staff is key to their individual success, as well as to the overall success of the research team.

## **Conclusion**

Through the challenges of conducting clinical research under COVID-19 restrictions, electronic and remote processes have been discovered and implemented that can be more efficient than some traditional onsite processes. It is important that we use this pandemic as a catalyst for change for the conduct of clinical research.

For example, research still is heavily dependent on paper-based documentation, especially when considering consent. As we see clinical research procedures in a new light, it is easy to envision the potential for growth in long-term adoption of electronic processes and continued exploration of new technologies that may make conducting research more efficient.

We have grown and are learning how to survive in the remote environment of a pandemic. It is crucial that regulatory bodies and all members of the research community continue to collaborate and provide support to sites as they explore the adoption of new technologies and electronic processes, even beyond COVID-19.

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GOOD MANAGEMENT PRACTICE

## **Conducting Clinical Trials in the Era of COVID-19: The Challenges of Maintaining Patient Safety and Data Integrity**

Carolyn Yanavich, PhD



The novel coronavirus behind the COVID-19 pandemic has affected and upended our lives in many ways. In the research and healthcare arenas, our focus has shifted from studying and treating a multitude of other conditions to the rapid development of novel treatments and vaccines for COVID-19. However, the need for developing interventions and therapeutics for other diseases persists.

With the primary goals of preserving the safety of research participants and staff, as well as maintaining clinical trial integrity, the [U.S. Food and Drug Administration \(FDA\)](#) and the [European Medicines Agency \(EMA\)](#) have provided guidance on the conduct of clinical trials during this unprecedented time. As of June 11, 2020, [there are 342,348 registered clinical trials](#) on ClinicalTrials.gov, most of which have been affected by COVID-19. While it's difficult to fully quantify the pandemic's toll on clinical research, many of these studies were disrupted by delayed starts, missed visits, or confounding adverse events.

Study sponsors are being forced to make challenging decisions about the future of the products in their clinical portfolios. While pausing new study enrollments and limiting the procedures performed at study visits minimizes the immediate risk of COVID-19, the long-term effects include incomplete datasets and delays in bringing new drugs to the market.

Further, with limited options for onsite monitoring visits, sponsors are relying on clinical monitors to remotely assess both the study conduct and the data. While these remote visits fulfill minimum reporting requirements, sites and sponsors must work closer with monitors to establish

easier methods for accessing and reviewing source documents electronically while maintaining participant confidentiality.

### **Sharing the Burdens**

Clinical research staff are facing challenges with novel standards for patient care, revised office hours and procedures, and an increased risk of staff and participants becoming infected with COVID-19. Social distancing is a challenge for busy clinics, and the target population for many therapeutic trials may also include those at greatest risk for acquiring COVID-19. Many sites have restrictions for in-person visits and have been forced to implement new ways to complete follow-up visits virtually. Clinical sites will need to reassess options for alternative waiting areas for patients, such as outdoor pavilions, tented areas, or in their cars, or separating those who are seeking preventative care versus those needing therapy.

Additionally, with the rising global demand for personal protective equipment, sites are facing new challenges with procuring these necessary supplies in order to protect themselves and to safely treat their study participants. These obstacles, when added to an already overtaxed staff, make it harder for our clinical sites to complete study procedures and tests and administer investigational products as prescribed.

As we await the availability of an effective vaccine for COVID-19, we must ask ourselves what the best strategies are for continuing to conduct clinical research studies. Can we ship study products to study participants rather than having them come to the clinic? How can we maximize our available technology to improve on telemedicine for research trials? Will sponsors proactively work with their clinical sites to understand their limitations and determine if study designs and procedures need to be amended or postponed?

### **Thorough Documentation Means Heightened Integrity**

Clinical research sites are tasked not only with keeping people safe from contracting COVID-19, but also with following and maintaining the standards of Good Clinical Practice. In following the old adage of “If it wasn’t documented, it wasn’t done,” sites are encouraged to document any

changes to their processes that were directly attributed to the pandemic and to ensure that all study deviations are clearly described.

Data for many of these affected studies will be produced in support of Investigational New Drug applications for products that will be submitted for licensure. While the regulatory agencies, including the FDA and EMA, have granted some study conduct flexibilities due to the pandemic conditions, any deviations from the original protocols for studies must be appropriately tracked and maintained onsite to ensure the integrity of the trial and its reconstruction, if necessary.

### **Everything's Connected**

While we tend to focus on the logistical burden of COVID-19 on conducting clinical research, the social distancing requirements that are employed to protect us may potentially have a negative effect on clinical trials data. For example, the measure of success of an HIV-1 vaccine is a decreased incidence of novel infections. However, with visits to restaurants, bars, concerts, sporting events, and other socialization activities being discouraged for so long during the pandemic, higher risk behaviors have also decreased, making it harder to determine if the HIV-1 vaccine is indeed effective, or if decreased infections are an indirect result of COVID-19 prevention efforts.

In summary, the way we conduct and manage clinical trials is evolving. While these changes can seem overwhelming, there is the positive potential for developing novel approaches to informed consent, streamlining laboratory procedures, increasing remote or telemedicine visits, or performing home healthcare for our more vulnerable study populations. Sponsors, sites, clinical monitors, and regulators must continue to keep an open dialogue on the best ways to conduct research trials both now and in the future.



**Carolyn Yanavich, PhD**, has more than 20 years of clinical research experience, including expertise in the principles and practices of clinical trial research, management, implementation, regulatory affairs, and laboratory science. She contributed this article through [Kolabtree](#).



SITE STRATEGIES

## **COVID-19 FDA Response: Guidance on Protocol Amendments and Clinical Study Reports in Affected Ongoing Trials**

Jack Modell, MD



As the world continues to navigate the many impacts of the novel coronavirus that causes COVID-19, the clinical research industry has seen an increase in new trials for the development of COVID-19-related treatments and products. On the other hand, some ongoing and planned clinical trials not related to COVID-19 have experienced operational interruptions, subsequently compromising the ability to collect meaningful, reliable, and accurate data, and in some cases jeopardizing the overall integrity of the trial.

These incidents have presented the need for protocol modifications to adjust for COVID-19 control measures and COVID-19 illness. The U.S. Food and Drug Administration (FDA) recently developed the “[FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency](#)” to offer advice on managing protocol amendments and deviations, as well as for documenting changes to the trial.

This column will discuss a few of the common challenges in conducting research that is not related to the pandemic during this time, as well as the current recommendations offered in the new FDA guidance. More detailed information on these and other COVID-19-related challenges can be found via the hyperlinks at the end of the column.

## **Subject Discontinuations and Assuring the Safety of Trial Participants**

The uncertainty of the evolving pandemic brings with it a variety of potential roadblocks to current trials, including a decrease in willing participants, travel restrictions, and staff reductions at study sites. Understandably, study participants are expressing a reluctance to visit healthcare settings out of concern of contracting COVID-19. As a result, some trials are experiencing an increase in missed visits or dropouts, and some studies have limited new enrollment and are focusing on subjects already in the trial.

FDA recognizes that protocol modifications may help mitigate the limitations imposed by the COVID-19 emergency, the nature of which will depend on many factors, including the disease under study, trial design, and specific difficulties that have been encountered in conducting the study. FDA underscores that sponsors must foremost continue to assure the safety of trial participants, as well as to maintain compliance with Good Clinical Practice (GCP) and minimize risks to trial integrity.

Depending on the specific circumstances of the trial, FDA states that sponsors—along with clinical investigators and institutional review boards (IRBs)—may determine that the protection of a study participant’s safety, welfare, and rights, while maintaining study integrity, is best served by any of the following:

- Continuing to participate in the trial as per protocol
- Discontinuing the administration or use of an investigation product
- Discontinuing participation in the trial
- Implementation of alternative processes or procedures that do not conflict with the requirements and limitations of the existing protocol
- Modifying study protocols and documenting the modifications in protocol amendments (protocol modifications should not be implemented prior to IRB approval unless required to eliminate or reduce an immediate safety risk for a subject, nor should they be implemented prior to consultation with the relevant reviewing division at FDA for modifications that involve study endpoints or statistical analysis)

## **Modifying Assessment Methods**

As study participants hesitate to visit healthcare facilities, the decrease in onsite visits makes it difficult to collect data from important assessments, including efficacy outcome measures and those required for patient safety, like visual examinations, vital signs, and procedures such as ECG or MRI. To help mitigate these challenges, FDA recommends that sponsors evaluate whether alternative methods to gather this information are possible. Examples include phone contact, virtual visits, in-home visits by a qualified professional, and use of local labs or diagnostic centers. These alternative methods are only suitable, however, in cases where the data can be objectively and adequately obtained and where subjects incur no increase in risk due to assessment delays or limitations.

## **Potential Impacts on Clinical Study Results**

Regardless of the specific modifications made to the assessment process, FDA emphasizes the need for sponsors to clearly document all changes to study conduct, the reasons behind them, and how COVID-19 influenced these changes. Many of these impacts, such as missed visits, may be captured as protocol deviations, while others may be documented as changes to the monitoring plan, findings in site visit monitoring reports, or data within the electronic data capture system.

Because changes in study requirements, allowances, and visit schedules (as well as missed visits or patient discontinuations) may fundamentally affect the ability of the study to yield valid and interpretable results, full documentation of all of these details in the clinical study reports is of utmost importance, as it allows both FDA and sponsors to look back to determine the extent to which the pandemic and associated modifications might have affected the overall outcome of the trial.

Additionally, the rationale for any changes to the protocol should be documented in all amendments. Further, as noted above, if an amendment to a study that is intended to provide data to support registration requires amending the data management and/or statistical analysis plans, or otherwise fundamentally changes the study design or analysis, FDA recommends consulting the appropriate review division before making the changes.

## Conclusion

As knowledge of the new coronavirus continues to evolve, sponsors must understand the practical limitations that exist and seriously consider what modifications might be necessary to assure patient safety, compliance with GCP, and the integrity of ongoing trials. Fortunately, today's technology has provided new ways of working around these challenges, with perhaps the most notable being the rise of video conferencing and telemedicine.

By considering FDA's recommendations and by complying with current regulations, sponsors can mitigate the risks on study conduct and integrity imposed by the current pandemic and continue working toward discovering new therapies for unmet medical needs.

Additional information on COVID-19-related challenges in drug development can be found via the following links:

- [Changes to Study Visits](#)
- [Choosing the Right Path Webinar](#)
- [Conduct of Ongoing Clinical Trials](#)
- [Development of COVID-19 Therapies: FDA Pathways](#)
- [COVID-19 Treatment Development Updates and Recent FDA Guidance](#)
- [Drug Shortages During the COVID-19 Pandemic](#)
- [Protocol Amendments](#)
- [COVID-19 FDA Response Site Management and Monitoring](#)
- [Maintaining Trial Integrity During COVID-19 and Statistical Rules of Thumb](#)

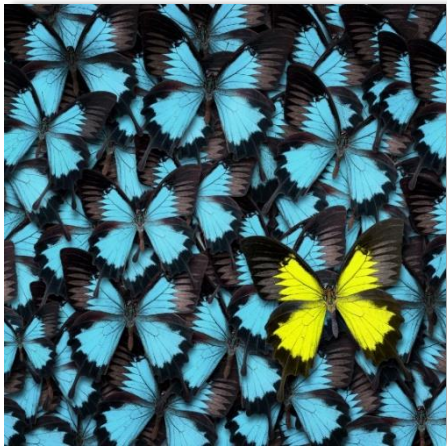


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RECRUITMENT & RETENTION

## Treasuring Your Exceptions in Rare Disease Research

Peter Coë



*Finding patients with a rare disease to take part in clinical research can be challenging; keeping them engaged in long research programs even more so. These patients, by definition, are few in number, so any one trial site may only have one or two patients per trial to enroll and keep engaged. So how do you treasure those exceptions—those participants who may make the difference between the trial being completed on time or not?*

### Understanding Rare Disease Patients

Patients with a rare condition often struggle to understand their disease fully. Many will have battled for years to get a diagnosis, and even then be faced with blank faces from healthcare professionals when they ask about alternative treatment options. Research and knowledge around rare diseases, even among specialists, can still be patchy and, as a result, many patients may not have seen anyone who is up to date on the latest knowledge concerning their condition.

Here are some comments shared by members of Raremark’s rare disease communities:

*“Having specialists scratching their heads, not knowing anything about the disease you have—it’s quite scary.”*

*“I had to suffer hours of excruciating pain before I could be taken seriously.”*

*“The feeling that you’re totally alone, dealing with a rare disease that no one seems to know anything about, is tough.”*

We recently asked members of our sickle cell community why they would take part in clinical research. They told us their top motivators were gaining insights into their own health, advancing medical science, and benefiting from the extra medical attention they would receive.

### **Top 10 Tips on Engaging Patients with Clinical Trials**

Based on hundreds of hours of conversations with patients who are interested in joining a clinical trial, here are 10 recommendations on engaging these rare exceptions in research.

1. A prompt response is vital to a new patient: within two days of a referral is ideal.
2. Please keep the patient's first appointment, if humanly possible. We have had hard-to-reach patients lose heart and turn their back on research after screening appointments were canceled more than once by study sites.
3. Use e-mail to agree on a time for a first phone call with referred patients, and to confirm a screening appointment. Patients often have busy lives outside the clinical trial, and will sometimes be working the same office hours as sites. They may not be instantly available to answer an unexpected call—or, more typically, they are unwilling to answer a call from a number they don't recognize.
4. If new patients prove hard to get hold of, or you want to see medical records before bringing them in for screening and you're too busy to do the chasing, trial partners may be able help. Tell the trial sponsor you need more support, and be precise about which records you really need to see.
5. Appreciate that many patients will be concerned about the effects of coming off an existing treatment, which is often a requirement of joining a trial for an investigational therapy. They may appreciate a conversation about how to mitigate the effects, and some reassurance about all the tests and procedures involved.
6. Underline what's expected of trial participants in the first conversation. People with a rare disease are often highly motivated to take part in clinical research, but may overlook the most

obvious requirements—particularly the number and frequency of visits to the study site and the logistics involved in getting there.

7. Before enrollment, explain what they can tell their friends and family about the trial. Many people living with a rare disease are used to posting frequently on social media, so they may need guidance on what details they should not post in order to preserve the privacy of their personal health information, the integrity of the trial, and the data being collected.

8. Ensure prompt payment of travel expenses and any honoraria. There's often a concierge service engaged to sort this on the study site's behalf, but the site coordinator should be familiar with what's available and how the patient can access it easily.

9. While they are on the trial, do share with patients any patient-friendly materials or blogs about living well with their condition. Create opportunities for communicating between study visits.

10. Where possible, take the trial to the patient, not the patient to the trial. If study procedures can be done just as well by a study nurse in a visit to the patient's home, or a video call can replace a site visit, then why not?

All of these tips would be followed routinely in an ideal world, but we appreciate that this often is not an ideal world and that many sites are working with inadequate resources. There are options for help, and it's worth a conversation with the trial sponsor when it's needed. Overall, it comes down to treating the patient's time and commitment with respect.

Communicate well, not only before enrollment, but also while patients are on the trial. (Timely reminders of upcoming appointments are a given.) If a site visit needs rescheduling, it's really appreciated if it can be done with forethought, not at the last minute. Birthday and seasonal greeting cards are also much appreciated—and a thank you card at the trial's end for taking part.

### **Patient Experience and How it Should Influence Trial Design**

Having a chronic illness can impact every aspect of a patient's life, and with a rare disease where specialist support is limited, the magnitude of the impact can feel enormous. Researchers need to

understand the everyday reality of living with the disease they are investigating before designing their clinical trial.

For example, some rare diseases lead to patients having to make multiple visits to the hospital, and the idea of taking part in a trial where they also have to visit the trial site frequently could be too much. Our sickle cell community reported visiting the ER about five times a year on average, with some visiting their primary healthcare provider more than 300 times in a 12-month period.

Trial sponsors already invest in travel reimbursement and, occasionally, in making accommodation available for patients near the trial site. Even better for patients with complex needs are more home visits, with nurses going to the patients to perform simple tests and procedures, and even to administer the trial drug.

### **Patient Experience During Trials**

The rise of the internet and social media has brought all kinds of individual patients and those in previously isolated groups closer together. That's particularly true for people living with a rare disease. They can now find and interact more easily with others affected by the same disease as they share their experiences. If patients have a positive experience during a trial, they are more likely to encourage others they are in contact with to take part in one in future.

When speaking to our sickle cell community, we found members generally had a positive experience with researchers in the trials they had taken part in, but felt the research staff didn't always answer their questions in ways they could understand.

Taking patients' needs into account in every aspect of the trial, including the language used and the care provided beyond the immediate demands of the protocol, will ensure better experiences and help to maintain engagement in research.

### **Encourage Trial Participation Through Understanding the Need**

Those responsible for planning rare disease trials need to better understand the world their prospective patients live in. Patient networks can do much to educate their community members



about the role clinical trials play in the medical world’s understanding of rare disease, and in the development of new and better treatments; trial sponsors can support these efforts through unrestricted educational grants. However, they can also do a lot more for themselves—through commissioning quality-of-life surveys for example, and by engaging patient panels before the protocol is set in stone—so they better understand the disease, the patient experience, and even what patients really want most from a new treatment.



**Peter Coë** is Co-founder and Director of Client Services for Raremark. He has 20 years of experience in health communications, with a focus on the development of treatments in areas of unmet medical need, particularly in rare disease. In the last 10 years he has led online campaigns to engage and recruit a wide range of hard-to-reach patient populations for quality-of-life studies and early- to late-stage clinical trials.