

Clinical Researcher™

The Authority in Ethical, Responsible Clinical Research

December 2020 (Volume 34, Issue 10)



**Reviews and Previews: Upbeat Investigations of Recent and Upcoming
Innovations in Clinical Research**

Clinical Researcher™

Association of Clinical Research Professionals

Editor-in-Chief

James Michael Causey
mcausey@acrpnnet.org
(703) 253-6274

Managing Editor

Gary W. Cramer
gcramer@acrpnnet.org
(703) 258-3504

Director, Advertising & Exhibition Sales

Tammy B. Myers, CEM
tammy.myers@acrpnnet.org
(703) 254-8112

Media Kit

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

For membership questions, contact ACRP at support@acrpnnet.org or (703) 254-8100.

Editorial Advisors for This Issue

Suheila Abdul-Karrim, CCRA, CCRT, FACRP
(Freelancer)

Staci Horvath, CCRA
(Gradalis, Inc.)

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

Jerry Stein, PhD, ACRP-CP
(Summer Creek Consulting, LLC)

For information on writing for *Clinical Researcher*, visit <https://www.acrpnnet.org/resources/clinical-researcher/> or e-mail gcramer@acrpnnet.org. Credit-granting Home Study tests are available at <https://www.acrpnnet.org/home-study/>, along with downloadable PDFs of the relevant articles and questions. The test from this issue should be online in January 2021.

Table of Contents

4 Executive Director’s Message—A Spring of Hope from Our Winter of Despair

Jim Kremidas

6 Chair’s Message—Staying in the Spotlight After the Storm Has Passed

Paul Evans, PhD

PEER REVIEWED

9 Quality by Design in the RECOVERY Trial (Randomized Evaluation of COVID-19 Therapy)

Brigid Mary Flanagan, BA, RN, CCRC, MSB

18 Biobanking and the COVID-19 Pandemic

Dr. Dina Avery

COLUMNS

23 Good Management Practice—Why the Future of Diagnostics Requires a New Approach to Trials

David Messina, PhD

28 IRB Insights (Part 1)—Views from an Independent IRB: A Q&A with Principal IRB’s Freddie Hughes and Debra Reed

Gary W. Cramer

32 IRB Insights (Part 2)—Press Releases, Predictions, and a Canadian Perspective on Research Ethics

Erica Heath, CIP; Dorothy Herbert, BSc, MAppSoc; Gary W. Cramer

38 Prescriptions for Business—Negative Shocks May Hit Twice in Pharmaceutical Development

Manuel Hermosilla

42 Science & Society—Clinical Research Saved My Life, Now it is Time to Make it Better

Al O. Pacino

45 Sites & Sponsors—The Future of Clinical Trials Will Require a Focus on the “Long Tail”

Kourosh Davarpanah, MS

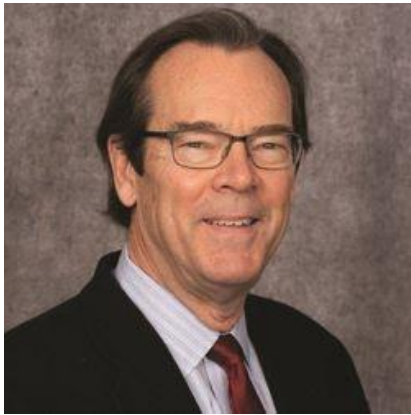
48 Trials & Technology—Five Ways Clinical Trials Will be Transformed in 2021

Alison Holland; Jena Daniels; Rasmus Hogleffe; Ingrid Oakley-Girvan, PhD, MPH;
Dr. Michelle Longmire

EXECUTIVE DIRECTOR'S MESSAGE

A Spring of Hope from Our Winter of Despair

Jim Kremidas



Charles Dickens clearly wasn't anticipating the year 2020 when he began writing his epic 1859 novel *A Tale of Two Cities* with the sentiment, "It was the best of times, it was the worst of times." By most measures, this year has been far heavier on the latter, beginning with a global pandemic and ending with a very fractious presidential campaign. And while the clinical trial industry has made exciting strides with COVID-19 vaccines in recent months, it's clear we're going to be struggling with this pandemic well into 2021 by even the most optimistic projections.

However, those who quote the first part of Dickens' most famous opening sentence often don't quote the rest of it. I think it's quite an apt description of 2020. Dickens goes on to write, "it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair."

We've seen all of that and more in what I'd charitably call a memorable 2020. In my final message for this year's run of *Clinical Researcher*, I'd like to focus on one shining positive: the conduct and contributions of you, the clinical trial professionals of the world. Through this unpredictable, frustrating, "let's never do that again" kind of year, the clinical trial workforce has risen to the challenge and brought a renewed sense of hope to people everywhere.

Clinical trial professionals exhibited an amazing ability to pivot in early 2020 as the COVID-19 pandemic began to spread. Leveraging the best of new technologies, embracing concepts such as decentralized trials and real-world evidence, all of you, working with the U.S. Food and Drug Administration and other regulatory agencies, made incredible and life-saving adjustments in the way trials are conducted.

Your inspiring hard work is already paying dividends. The clinical trial industry responded to this health crisis with true “warp speed” while maintaining important safety checks and working hard to ensure data integrity and trial efficacy. You, the clinical trial professionals of 2020 and 2021, turned some of the worst of times into some of the best of times in terms of human compassion, ingenuity, and tangible success.

On behalf of the entire ACRP team, it’s an honor to help support the invaluable work each of you do. I wish you a safe and relaxing holiday season and look forward to seeing the amazing things you will accomplish in 2021.

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

CHAIR'S MESSAGE

Staying in the Spotlight After the Storm Has Passed

Paul Evans, PhD

"It is not the strongest or the most intelligent who will survive but those who can best manage change." – Charles Darwin



Scholars are still debating whether Darwin actually said this, or if it was said later by someone interpreting Darwin's work. Either way, I think 2020 has shown there's strong evidence to support the idea.

As this challenging year winds down, I'm reflecting, like many of you I suspect, on what we've collectively endured and how it has impacted us. My reflections are also tinged with a touch of wistfulness as I step down as Chair of ACRP's Association Board of Trustees at the end of this month.

Elsewhere in the virtual pages of this month's *Clinical Researcher*, ACRP Executive Director Jim Kremidas quotes my countryman Charles Dickens' famous line, "It was the best of times, it was the worst of times" to summarize 2020. Certainly, the worst of times, as it were, have been on full display in the U.S., where we've recently passed 300,000 COVID-19 deaths. However, I'd like to focus more of my final column on the positives we've seen this year, starting with the heroic work of the clinical trial workforce.

The pandemic may have provided many challenges to us all, but we as an industry have never been more in the spotlight. Our contributions to the fastest development of a vaccine on record put us right in the public eye in a very positive light. As I've noted in earlier columns, as an industry we need to build on that and make sure we encourage the general public to remain

interested and engaged in drug research and not revert back to our normal secretive ways. Silos are so 2019!

The nightmare of COVID-19 has also showed us the dreamwork of teamwork. If the coronavirus vaccine development demonstrated one thing, it is what can be achieved when we all act with a unity of purpose toward achieving a single goal. Before this public health crisis, too much of drug research felt like everybody working against one another; COVID-19 changed that in 2020, and I fervently hope we retain that spirit of cooperation in 2021 and beyond.

Keeping on Track (with Pivots)

The mission of ACRP has never been more critical. Good research requires good people, and our mission is to support the development of the people who deliver new drugs (protecting patients as a result) and to encourage new people to enter our industry.

Like it has on everyone and everything else, COVID-19 has had a huge impact on your Association. As a team, we had to pivot and adapt in a number of areas. For example, we had to cancel our annual meeting scheduled for Seattle in April. Each year the meeting is an exciting way to recharge batteries, swap ideas, renew acquaintances—not to mention its significant financial importance to ACRP. Well, COVID-19 took all that from us.

So, Jim Kremidas, Bridget Gonzales, director of training and professional development, and others at ACRP pulled together and learned on the fly how to prepare and conduct virtual meetings to help defray some of that loss financially and educationally. I participated in some of the meetings and viewed a large portion of them, and I was very impressed with the end product. I heard from many of you members, too, remarking on the quality of the sessions, the moderation by Editor-in-Chief Michael Causey, and the overall production.

Kevin McCourt, ACRP's chief operating officer, spearheaded the rapid and successful application for a Payment Protection Program loan earlier this year to support ACRP's finances. We received the loan, which helped us avoid making any cuts in staff or product offerings. I can also happily report that the loan was recently forgiven because we honored the terms it set. Kudos to Kevin and team for securing such a timely fiscal shot in the arm for your Association.

I'd also like to salute the other ACRP board members I had the chance to work with this year. Again, COVID-19 changed the nature of our interactions—for example, we had to pivot from in-person meetings to Zoom and phone meetings. Throughout the difficult transition, I was impressed with the intelligence and consistently professional conduct of my colleagues. I thank each of them for their valuable contribution to ACRP and the broader clinical trial mission.

Better Days Ahead

Thanks to this amazing industry, vaccines are on the way to help us defeat COVID-19. I know this has been a difficult year, but there's light at the end of the tunnel, and I hope everybody has the best possible holiday season.

It was an honor and a privilege to be able to serve the membership this year as Chair. Thank you for allowing me the opportunity.

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

Clinical Researcher—December 2020 (Volume 34, Issue 10)

PEER REVIEWED

Quality by Design in the RECOVERY Trial (Randomized Evaluation of COVID-19 Therapy)

Brigid Mary Flanagan, BA, RN, CCRC, MSB



If you are not following the progress of the RECOVERY trial, you should be. It is a great example of quality by design (QbD) in action. The trial is a randomized controlled study to evaluate potential treatments for COVID-19. The lead investigator is Peter Horby, Professor of Emerging Infectious Diseases and Global Health at Oxford University in the United Kingdom.

The first draft of the protocol was available on March 10, 2020. It was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the appropriate ethics committee on March 13, received regulatory approval on March 16, and received ethics approval on March 18. The first patient was enrolled on March 19, and by April 1, 1,000 patients had been enrolled. As of this writing, 15,303 participants have been randomized at 176 sites.

The trial is designed to have the least possible impact on hospital personnel. It has already demonstrated that there is no clinical benefit from the use of hydroxychloroquine in hospitalized patients with COVID-19, and that low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19.

This trial has demonstrated that when you build quality into the design of your trial, eliminate complexity, and have the buy-in of a broad spectrum of stakeholders, you can achieve success. This trial has changed clinical practice, including for pregnant women.

The Protocol

The design, conduct, and analysis of the trial is focused on issues that might have a material impact on the well-being and safety of study participants (hospitalized patients with suspected or confirmed SARS-CoV-2 infection) and reliability of results that would inform the care for future patients.{1} An additional factor to consider, in the context of this trial, is the well-being of staff, since SARS-CoV-2 is a transmissible disease.

A co-director of the study is Martin Landray, PhD, FRCP, Professor of Medicine and Epidemiology at the Nuffield Department of Population at the University of Oxford. In 2012, he argued for QbD to be factored into clinical trials whereby those responsible for the overall conduct of a trial would identify the critical aspects that, if not performed correctly, would threaten the protection of patients or the integrity of results.{2}

When developing the protocol, in early 2020, there were no approved treatments for COVID-19, the disease caused by the novel coronavirus which emerged in China in late 2019. The UK New and Emerging Respiratory Virus Threats Advisory Group advised that several possible treatments should be evaluated, including low-dose steroids, hydroxychloroquine, and lopinavir-ritonavir.

The inclusion criteria were unambiguous: Aged ≥ 18 , admitted to hospital with proven or suspected SARS-CoV-2 infection (“suspected” infection was an early modification to the protocol). Physicians recognized the clinical syndrome, but there were delays in getting test results. They also recognized that not all tests are positive initially and that, if you are going to treat these patients, it makes sense to start treatment early, not two days later.

Eligible patients are consented by the admitting physicians. The patient is then randomized to one of several treatment arms, each of which will be given with the usual standard of care. A prescription for the assigned treatment is submitted to the hospital pharmacy, which manages

supplies centrally. The main outcomes are death, discharge, the need for ventilation, and the need for renal therapy at 28 days post randomization.

It is an adaptive design trial, with the results being monitored on an ongoing basis by an independent data monitoring committee (DMC) to assess whether the randomized comparisons in the study have produced evidence that is strong enough to affect treatment strategies. Trial arms that demonstrate lack of efficacy are discontinued and new arms are added as other evidence emerges of potentially beneficial treatments. Of interest is that pregnant women are not excluded and there is no upper age limit for trial participants. The oldest participant to date has been 109 years of age. {3}

As of the end of September 2020, Version 9 of the protocol was open to enrollment. From Version 6 onwards, a factorial design (used to understand the effect of two or more independent variables) has been used so eligible and consenting participants can be randomized to one of the treatment arms in Randomization A and, simultaneously, to one of the treatment arms in Randomization B. {4} For Randomization A that can be:

- i. No additional treatment
- ii. Corticosteroids (pediatrics only)
- iii. Azithromycin
- iv. Intravenous immunoglobulin (pediatrics only)

For Randomization B, eligible patients will be randomly allocated between the following treatment arms (provided they have consented and there are no contraindications):

- i. No additional treatment
- ii. Convalescent plasma
- iii. Synthetic neutralizing antibodies (provided by Regeneron)

Patients with progressive COVID-19 as evidenced by hypoxia (oxygen saturation < 92% on room air) and an inflammatory state (C-reactive protein (CRP) \geq 75mg/L) can be randomized a second time to either:

- i. No additional treatment
- ii. Tocilizumab

The larger the numbers randomized, the more accurate the results will be. Tellingly, enrollment slowed down in the summer of 2020 as the numbers of patients being hospitalized decreased. Enrollment has picked up in September and October, as the number of infections began to resurge across the UK.

Trial Processes

In line with QbD principles, all trial processes have been greatly simplified to minimize the burden on frontline staff in busy hospital settings who have been stretched to the limit during the pandemic. The University of Oxford is the trial sponsor, with trial coordination coming from a Central Coordinating Office (CCO) staffed by members of two registered clinical trial units. The CCO oversees regional coordinating centers which, in turn, assist with the selection of local centers. The study is conducted at multiple hospitals within the local regions.{4}

The consent for participation is less than five pages long and is available in multiple languages reflecting the diversity of the UK population (e.g., Polish, Urdu, Bengali, etc.). Training is all available online and must be completed before a site is activated. Training requirements are dependent on one's role in the study; for example, all are required to complete background training and those obtaining consent and/or performing randomization have additional training modules for those duties.

A one-page case report form (CRF) is completed online prior to randomizing a subject. A second CRF is completed at death, discharge, or at 28 days, whichever comes soonest. Information collected includes:

- Vital status
- Hospitalization status
- SARS-CoV-2 result
- Use of ventilation (number of days and type)

- Use of renal dialysis or hemofiltration
- Documented new major cardiac arrhythmias
- Use of any medications in the RECOVERY trial or other purported COVID-19 treatments (e.g., remdesivir)

Additional information is collected in the first 72 hours for the first 200 subjects randomized in Main Randomization B (no additional treatment vs. convalescent plasma and no additional treatment vs. synthetic neutralizing antibody):

- Sudden worsening of respiratory status
- Severe allergic reaction or other infusion reaction
- Temperature $>39^{\circ}\text{C}$ or $\geq 2^{\circ}\text{C}$ above baseline
- Sudden hypotension
- Clinical hemolysis
- Thrombotic event

In addition, Serious Hazard of Transfusion (SHOT) reporting is conducted for all patients receiving convalescent plasma for the full duration of the study. All the information collected for the study is in the medical record and would routinely be documented absent trial participation.

For data and safety monitoring, the focus is on events that, based on a single case study, are highly likely to be related to the study medication (e.g., anaphylaxis, Stevens-Johnson syndrome, or bone marrow failure), where there is no other plausible explanation. Events that are the consequence of COVID-19 and common events which are the consequence of conditions which existed prior to randomization are exempt from reporting.

Monitoring is done remotely by the CCO. Onsite monitoring will only be considered if a training need is identified or the results of central statistical monitoring suggest there might be an issue. No routine source data verification is taking place. Given that there is a pandemic, site visits would not be appropriate, as they could increase the risk of spreading infection. {4}

The protocol, the informed consent, sample CRF pages, training materials, and patient information sheets are all available for public viewing on the RECOVERY website at www.recoverytrial.net.

The Stakeholders

The effort to date reflects the strong collaboration among the various stakeholders. These include the National Health System (NHS), the MHRA, the ethics committee, the Health Research Authority, and the Chief Medical Officers of England, Wales, Scotland, and Northern Ireland, who wrote to all physicians across the UK requesting their support with enrollment and encouraging a default position where every eligible patient is offered enrollment in a clinical trial.

Strong evidence requires large numbers (e.g., 2,000 subjects per arm).{5} The lead investigator had hoped to enroll 1,000 subjects a week, but that has not always been possible. However, the strong national (and international) coverage, as well as the recruitment successes to date, have resulted in requests for inclusion from other national health authorities; discussions are ongoing with Vietnam, Indonesia, and Nepal.

The aforementioned website has a section dedicated to patients. There is a video in which the co-investigators for the study describe each of the drugs being investigated as possible treatments for COVID-19 and a list of frequently asked questions.

Results to Date

The most consequential results to date have been that low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19 and one fifth in other patients receiving oxygen alone. A press release issued in June 2020 indicated that 2,104 patients randomized to receive dexamethasone 6mg once a day, either by mouth or intravenously, were compared to 4,321 randomized to usual care alone. In the press release, co-investigator Landray said: “Since the appearance of COVID-19 six months ago, the search has been on for treatments that can improve survival, particularly in the sickest patients. These preliminary results from the RECOVERY trial are very clear—dexamethasone reduces the risk

of death among patients with severe respiratory complications. COVID-19 is a global disease—it is fantastic that the first treatment demonstrated to reduce mortality is one that is instantly available and affordable worldwide.”{6} The trial results were subsequently published in *New England Journal of Medicine (NEJM)* on July 20, 2020.

The independent DMC concluded that there was no beneficial effect of hydroxychloroquine in patients hospitalized with COVID-19. A separate June 2020 press release {7} indicated 1,542 patients randomized to hydroxychloroquine were compared to 3,132 randomized to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality and no evidence of beneficial effects on duration of hospital stay or other outcomes. Those results were subsequently published in the *NEJM* on October 8, 2020. The conclusion was the same for the lopinavir-ritonavir arm, and that arm was discontinued. Those results were published in *The Lancet* on October 5, 2020.

Discussion

The RECOVERY trial is a great example of what can be accomplished when you have buy-in from all stakeholders. There is no negotiation on the contract, no payments to investigators, and no recruitment targets.{8} Indemnity is addressed in the protocol (the university has a specialist insurance policy in place which will operate in the event of any participant suffering harm because of their study participation).

The protocol objectives are clear; the primary objective is to estimate the effects of study treatment on all-cause mortality within 28 days of randomization. The secondary objectives are to investigate the effect of study treatments on the duration of the hospital stay, the need (and duration) of ventilation, and the need for renal replacement therapy. There are no tertiary or exploratory endpoints. Trial procedures are greatly streamlined, and randomization is done online. The confirmation of the allocated treatment can be downloaded and printed. Data entry is minimal. Follow-up information is collected at one timepoint only (Day 28) and can be done by phone, in person, or electronically.

Usually in studies, participants are assigned a study number and the trial sponsor does not know their identities. In this case, the participant's NHS number is collected along with some other personal details. The informed consent explicitly states that the researchers may request additional medical information that is maintained in local or national records for up to 10 years following the scheduled follow-up period. As the long-term sequelae of COVID-19 are unknown now (10 months into the worldwide pandemic), and eligible participants may be receiving investigational agents, this reservoir of data could potentially be a great source of information. This is one of the benefits of a national healthcare system.

Other points of interest are the very broad inclusion/exclusion criteria. It is refreshing to see that participants are not excluded because their body weight exceeds 30kg/m², they are pregnant, or they are more than 65 years of age. With respect to co-morbidities, if, in the opinion of the investigator, study participation would put the patient at significant risk, they should be excluded. As the trial is for hospitalized patients and there are no known cures, participation in the RECOVERY trial may be a patient's best option for making a good recovery.

Conclusion

The RECOVERY trial is a great example of QbD in action. For people who struggle with the concept of QbD, this is an opportunity to learn from one of the original proponents for QbD in clinical trials, Professor Martin Landray. All the materials are available for access by the public, including the protocol, informed consent, patient information materials, sample CRF pages, and the statistical analysis plan. This transparency is to be commended.

The protocol is easily understood (33 pages in total). The informed consent is short and to the point. Trial processes have been simplified. Data collection is minimal. The numbers enrolled will depend on the duration of the pandemic. A DMC is reviewing the data on an ongoing basis to determine the effect of treatments on mortality that is strong enough to affect clinical practice. Most importantly, the RECOVERY trial has broad support from all a variety of stakeholders, including the MHRA and NHS clinicians, in the UK.

To date, dexamethasone (first made in 1957, off-patent and widely available around the world) is the only treatment identified to have benefits for patients receiving respiratory support. Those results have changed the management of hospitalized patients worldwide.

As research professionals, we can all learn something from this trial. The pandemic has been a catalyst for change in how trials are conducted. Let us hope we can keep that momentum going forward.

References

1. <https://www.recoverytrial.net/files/recovery-protocol-v9-1-2020-09-18.pdf>
2. Landray MJ, et al. 2012. Clinical Trials: Rethinking How We Ensure Quality. *Drug Information Journal* 46(6):657–60.
3. <http://www.francesoir.fr/politique-monde/interview-exclusive-martin-landray-recovery-hydroxychloroquine-game-over-uk>
4. <https://www.recoverytrial.net/files/recovery-protocol-v9-1-2020-09-18.pdf>
5. Letter dated 06 May 2020 from NHS Chief Medical Officers to their Colleagues. <https://www.recoverytrial.net/>
6. <https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19>
7. <https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19>
8. <https://www.recoverytrial.net/for-site-staff/site-set-up-1/recovery-trial-faqs-for-study-sites>

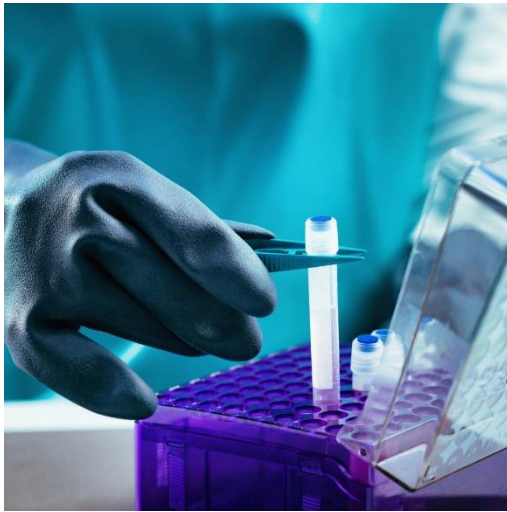


Brigid Mary Flanagan, BA, RN, CCRC, MSB,
(bflanagan@orielresearchservices.com) is Managing Director of Oriel Research Services in Drogheda, Co. Louth, Ireland.

PEER REVIEWED

Biobanking and the COVID-19 Pandemic

Dr. Dina Avery



No one was prepared for the significant impact COVID-19 is having on global healthcare and biobanking operations. Once COVID-19 arrived across the world, few hospitals and biobanks were fully ready for the influx of infected patients and high death rates associated with the virus.

COVID-19 has caused global biobanks to purchase more personal protective equipment (PPE) in order to protect their employees, and even employees had to be monitored closely for possible COVID-19 symptoms. Biobanks had to communicate and search globally to order needed supplies to collect and store specimens rapidly. They also had to become innovative in their practices to accelerate digital communication to healthcare facilities, regarding the number of patients being tested and to communicate each patient's results.

For these and other reasons, COVID-19 has provided a vivid example of why and how biobanks are crucial to advancing clinical trials involving vaccine development and longitudinal studies involving outcomes data.

COVID-19 Biobanking, LIMS, and Regulatory Concerns

Virtual biobanks are now essential, especially since globally there were 43,341,451 confirmed COVID-19 cases and 1,157,509 deaths due to the virus as of October 27, 2020.^{1} According to the Centers for Disease Control and Prevention (CDC), the digital tools being utilized to capture routine health data during this pandemic include District Health Information Software ([DHIS2](#)),

the Surveillance, Outbreak Response Management, and Analysis System ([SORMAS](#)), Go.Data, Open Data Kit, Epi Info, CommCare, KoboToolbox, and Excel.{2} Laboratory Information Management Systems ([LIMS](#)) are being widely utilized among biobanks located in North America, Europe, China, Japan, Southeast Asia, India, Central America, South America, and elsewhere.{3}

No digital tool will be effective without the needed data being stored in LIMS. Global biobanks are extremely useful during the current pandemic because they enable global researchers to access source material and data needed to perform clinical research and trials, irrespective of the actual geographical location of the COVID-19 specimens.{4} This aids researchers' in-depth studies of COVID-19, as they seek to develop better treatment options and vaccines to eradicate this virus.

Since travel to and from various countries is limited during the pandemic, it is necessary to utilize data-sharing solutions to review data and outcomes from diagnosed COVID-19 patients. Global biobanks working within the same consortium must communicate and narrow down the data to be collected via a questionnaire by the biobanking employee. It is vital to collect each diagnosed patient's pathology results, medical history, symptoms, and other needed outcomes data. The collected data from each specimen can be entered into a database such as LIMS.

LIMS will definitely allow global biobanks to improve workflows by managing sample collection, sample distribution, patient scheduling, test reporting, and data analysis. Global biobanks utilizing LIMS must follow international regulatory guidelines issued by the United National Educational, Scientific, and Cultural Organization's ([UNESCO](#)'s) International Declaration on Human Genetic Data, which provides principles related to collecting, processing, and storing human proteomic data and genetic data.{4}

Additional guidances are provided by the International Society for Biological and Environmental Repositories ([ISBER](#)), Clinical Laboratory Improvement Amendments ([CLIA](#)), International Organization for Standardization (ISO) [15189:2021](#), and the Health Insurance Portability and Accountability Act (HIPAA).{4,5} Biobanking employees must be trained by their management

team in reviewing these regulatory guidelines to maintain compliant and efficient quality management systems and biobanking practices.

Risk Management

Biobanks have become innovative by streamlining processes to meet the public health demand. We see more biobank and laboratory employees working in outdoor locations due to the number of daily COVID-19 tests being conducted. The demand for biobanking employees is continuously increasing because they are needed both at these sometimes remote locations and within the regular facilities.

Many students, employees of large organizations, medical professionals, and others are now required to undergo regular COVID-19 testing, even when not showing any signs of the virus. Specimens are even collected from patients already hospitalized with COVID-19. This alone has increased the labor force needed to maintain efficient biobanks.

No matter where a biobank is located, everyone involved in it must practice effective risk management strategies. Biobank employees must safely handle all fresh and frozen biospecimens as infectious materials, which minimizes potential exposure to those collecting and transporting them. Appropriate, safe handling practices also protect the general population. {6}

Further, it is required that all biobanking employees wear PPE and have the necessary equipment to process and store the collected specimens within a sterile environment. International Air Transport Association ([IATA](#)) Dangerous Goods Regulations provide guidance on packing and shipping specimens. {7} Environmental Protection Agency–registered disinfectants must always be readily available and proper sanitation protocols must be followed.

Conclusion

The COVID-19 pandemic has increased the money generated by biobanks. The biobanking market is expected to generate \$49.46 billion annually by 2026. {8} As a result, the LIMS market is expected to reach \$896.8 million annually by the end of that same year, compared to \$601.7 million generated in 2019. {3}

Due to large number of clinical trials related to COVID-19, biobanks are essential in collecting and storing biosamples such as plasma, serum, DNA and RNA, clinical data, and genomic data. Researchers want to know more than just if a specimen is positive or negative for COVID-19. Collected data related to each COVID-19 specimen will allow researchers to develop evidence-based strategies, design treatment protocols and predictions based on precision medicine, and share lessons learned.

No one can really predict what is ahead globally, due to the predicted second wave of the pandemic and the unknown effectiveness of future vaccines to be distributed globally. However, biobanking employees are essential workers and their role is continuously evolving since COVID-19 is a new virus. It is imperative for biobanks across the globe to continue to communicate, streamline processes, learn from each other, and work together with other medical professionals toward improving the relevance of their contributions to scientific research and fostering a sustainable network expansion that will lead to novel COVID-19 biobanking strategies.

References

1. World Health Organization. 2020. WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int/>
2. Centers for Disease Control and Prevention. 2020. Guide to Global Digital Tools for COVID-19 Response. <https://www.cdc.gov/coronavirus/2019-ncov/global-covid-19/compare-digital-tools.html>
3. Market Watch. 2020. Global LIMS Market Size 2020 Trend and Opportunities, Market Share, Analysis, CAGR and Value Chain Study, Showing Impressive Growth by 2026. <https://www.marketwatch.com/press-release/global-lims-market-size-2020-trend-and-opportunities-market-share-analysis-cagr-and-value-chain-study-showing-impressive-growth-by-2026-2020-09-03>
4. Shonali P and Chatterjee MK. 2020. Data Sharing Solutions for Biobanks for the COVID-19 Pandemic. *Biopreservation and Biobanking*. <https://doi.org/10.1089/bio.2020.0040>
5. CloudLIMS. 2020. Deploy in Less than a Week: Preconfigured COVID-19 Testing, Research and Biobanking Workflows Using CloudLIMS, an in the Cloud COVID-19 LIMS. <https://cloudlims.com/industries/covid-19-lims-software.html>
6. Lankes HA and Makhlof H. 2020. Biospecimens Collection During the COVID-19 Pandemic: Considerations for Biobanking. *American Journal of Clinical Pathology*. <https://doi.org/10.1093/ajcp/aqaa171>
7. Therapak. 2020. Category B and IATA Packaging. <https://therapak.com/catalog/specimen-shipping-systems-iata/category-b/>

8. Globe Newswire. 2020. Biobanking Market to Reach \$49.46 Billion by 2026; Recent Breakthrough Concepts Have Indicated Potential in Covid-19 Vaccine, Says Fortune Business Insights. <https://www.globenewswire.com/news-release/2020/06/18/2050309/0/en/Biobanking-Market-to-Reach-49-46-Billion-by-2026-Recent-Breakthrough-Concepts-have-Indicated-Potential-in-Covid-19-Vaccine-says-Fortune-Business-Insights.html>

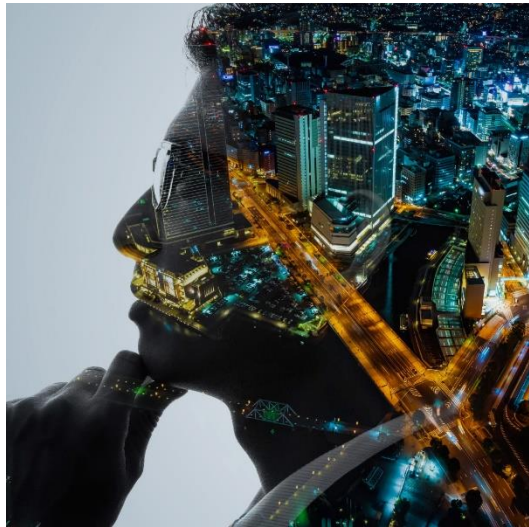


Dr. Dina Avery, (dvavery@uab.edu) is an Assistant Professor and Associate Scientist in the School of Health Professions at University of Alabama at Birmingham.

GOOD MANAGEMENT PRACTICE

Why the Future of Diagnostics Requires a New Approach to Trials

David Messina, PhD



Scientific and medical research is an investment in our future. We're all keen to live long, healthy lives and most of us are willing to empower physicians to make educated decisions about our care if and when we do become ill. Further, as we've seen from hundreds of years of scientific advancement, medicine is not a short-term investment. When a new drug or medical device comes to market, it builds on decades of basic science research, translational research and development, and clinical studies.

In the early 2000s, [economists evaluated federal investments in medical and health research](#) and found “that the returns from the national investment in medical research—both in the past and what is likely to be delivered in the future—are exceptional and far greater than is appreciated by either policy makers or the public.” That said, public and private investors alike know there is no fast-track to success; no magic pathway that results in breakthroughs faster or more often.

Scientific and medical research is rigorous, methodical, and fraught with failure. Often, however, these failures come with great learning opportunities, which help yield future successes.

Learning from Clinical Studies

One such learning opportunity is centered on the clinical studies that help move therapeutics and diagnostics out of the research lab and into clinical practice. Drug trials have exploded in the last decade, particularly in immune oncology, with more than 1,000 trials initiated in the U.S. alone

last year, according to Kantar Health. This has spurred significant innovation in the therapies available for patients.

However, as we enter an era of more precise medicine, many of the therapies being developed work only in a subset of the patient population. This means there is a need for the development of a diagnostic approach for selecting patient populations who will respond well to the therapy.

At first, the industry prioritized this at the same time as the drug, developing the companion diagnostic in parallel and resulting in an on-label test that is required for safe use of the drug. An example of this is the use of a PD-L1 immunohistochemistry (IHC) assay to select patients for anti-PD-1 immunotherapies. While the intent behind this approach is sound, I would argue that it has unintentionally laid the foundation for a lack of innovation in diagnostic development.

For example, in some indications where PD-L1 IHC is currently the approved companion diagnostic device, such as recurrent and metastatic squamous cell carcinoma of the head and neck, clinicians have little to no confidence in its ability to predict response. So, rather than guiding treatment decisions, it's seen as necessary but unproductive.

Despite broad awareness of this situation, the industry has overwhelmingly focused on expanding the indications approved for treatment with anti-PD-1 therapies, and has not given sufficient consideration to improving our ability to predict response and replacing the on-label diagnostic. So it is that, as with many other facets of medical research, our failures have taught us that there is room to improve. The future of diagnostics requires a new trial approach—particularly in oncology.

Driven by Innovation

While IHC has provided decades of invaluable information, it is far from being the most sensitive or specific methodology we have at our disposal. Further, the reproducibility of the technology poses major challenges, as was evaluated in the [Blueprint Study](#). So, when we design clinical studies—either for companion diagnostics or independent diagnostics—I would argue we should be driven by the most innovative, informative tools we have, not just what has worked well in the past and represents a “safe bet.”

There are many other technologies available that have demonstrated they can generate valuable biological insights for oncology biomarkers. By moving these from the research space and into our suite of options for diagnostic development, we are expanding our arsenal in our fight against cancer. Further, when we look to more advanced technologies, we have the benefit of moving from a single-analyte snapshot to a more multidimensional, multi-analyte approach, which provides a more holistic view of the patient's disease.

Examples of other technologies that should be considered include other imaging technologies with improved sensitivity and specificity, namely, immunofluorescence and mass cytometry. If spatial information is not biologically relevant to the biomarker to be measured, then technologies using next-generation sequencing (NGS) or polymerase chain reaction (PCR) are an excellent option. This umbrella is vast and covers DNA measurements such as tumor mutational burden (TMB) and microsatellite instability (MSI), as well as RNA measurements including gene expression, immune profiling, and predictive immune modeling.

Each of these have plentiful translational research that demonstrates their potential use as oncology biomarkers, and should be considered for diagnostic development in both the companion and predictive diagnostic setting. Examples include [TMB across multiple solid tumor types](#), [co-testing MSI by PCR and dMMR by IHC](#), and the relationships between [MSI, TMB, and PD-1/PD-L1 expression](#).

With the goal of precision medicine comes the need for multidimensional technologies. In the immunotherapy example, measuring holistic immune response at the site of the solid tumor is paramount to improving our ability to predict tumor response and [has been shown to perform better than IHC alone](#). The future of diagnostic trials must leverage innovative technologies that can provide better insight into the complex biology of each patient.

Decentralized, Yet Harmonized

Diagnostic clinical studies are challenged by the same barriers to success that have been described for all clinical trials, including recruiting sufficient diversity in cohorts to represent the general patient population, ensuring compliance of patients, and confirming sites are following

protocols identically. It's certainly clear that decentralized trials are most effective for recruiting a more diverse patient population, but you might be concerned that this approach increases the latter challenge of site management.

In fact, each of the barriers listed can be reduced when a sponsor partners with a contract research organization (CRO) that is well-versed in running highly virtual trials. These CROs are equipped with platforms to provide remote monitoring, electronic patient consenting, and electronic data capture. This model even enables individual investigators, who may be passionate about science and improving patient outcomes but are not located in academic institutions with dedicated clinical trial staff, to enroll patients for participation in a clinical trial.

A virtual trial platform also allows for sponsors to leverage direct-to-patient engagement. By extending trial sites beyond large academic centers to sites local to patients, we enable maximal diversity in recruitment, streamline participant engagement, and help ensure improvements to patient compliance. This approach to diagnostic trials, especially those that are non-interventional and may not require additional hospital visits, would allow patients to participate in a clinical trial no matter where they live, what their socioeconomic status is, and who their treating physician is.

The future of diagnostic trials must be decentralized and supported by CRO partners who can keep sites and protocols harmonized.

Independent and Equally Impactful

Building a diagnostic that improves patients' care paths and clinical outcomes should not be considered an afterthought, or only considered when bringing a new drug to market. Lessons learned during the development of predictive diagnostics for new therapies demonstrate that this approach has value for all therapies available. By developing predictive diagnostics for decision points along multiple care paths rather than for only one therapy, we move closer to the precision medicine paradigm where these technologies will empower physicians to understand the potential outcomes for the myriad of therapeutic options available to them.

Robust clinical studies for biomarkers should be prioritized not only during drug development, but also for therapies already on the market. The diagnostics being evaluated for predicting tumor response to anti-PD-1 therapy represent great progress post-therapy approval. However, we should not stop with building diagnostics for immunotherapies alone. Helping physicians make decisions about chemotherapy, radiation therapy, and combination therapies using diagnostic tools will not only improve patient outcomes, but will provide financial advantages for payers, patients, and the entire healthcare ecosystem.

Conclusion

As members of the clinical research community, we're all aware that the stakes of our investment in medical and healthcare research have never been higher. Scrutiny in how funds are spent, the rising cost of healthcare, and our aging population require us to find new ways of rising to meet these challenges.

A fixation on novel therapies alone will not allow us to meet our goals of matching patients with the most impactful treatment regimen. Expanding our efforts to focus on diagnostic innovation, and even on how and when we conduct the clinical studies that bring diagnostic technologies to market, is essential to delivering successful outcomes and closing the precision medicine gap.



David Messina, PhD, has spent the last 20 years in computational biology and human genetics. He contributed to the Human Genome Project at Washington University in Saint Louis, mapped disease genes at the University of Chicago, and co-developed the first comprehensive atlas of human transcription factor genes. As COO of Cofactor Genomics, he is the lead on all regulatory and reimbursement efforts for the company, driving the implementation of RNA-based diagnostics and their clinical application.

Clinical Researcher—December 2020 (Volume 34, Issue 10)

IRB INSIGHTS (PART 1)

Views from an Independent IRB: A Q&A with Principal IRB’s Freddie Hughes and Debra Reed

Gary W. Cramer



Consolidation has been the ongoing trend of the past decade or more where the providers of goods and services tied to the clinical research enterprise are concerned. One need look no further than the institutional review board (IRB) sector in recent years to see heavy levels of restructuring activity as firms vie to remain competitive in the face of many economic, regulatory, and societal challenges affecting research review and oversight.

Whereas some of the “giants” of the for-profit IRB world have grown by leaps and bounds—broadening their offerings nationally and internationally—through strategic mergers with and acquisitions of former rivals, other boards have remained independent and focused on more personalized services to a smaller client base. Such is the case at Principal IRB in Florida, as explained by Freddie Hughes, RN, CIM, Managing Partner, Operations, and Debra Reed, Managing Partner, Marketing, in the following Q&A.

ACRP: Can you share some details about the career path that brought you into the world of IRBs?



Freddie Hughes: For me, I see IRB work as a natural extension of my healthcare experience, and research as a branch on the tree of healthcare. Therefore as a registered nurse, it is understandable that more than a decade ago I developed a passion for the work of protecting individuals who are willing to participate in clinical trials. Research is a vital part of medical innovation, and the people who participate deserve to have an organization like Principal IRB helping to ensure that protections are in place.

ACRP: You call your company a “boutique IRB.” What does this mean in terms of your areas of specialization, and how rare is your business model in today’s IRB environment?



Debra Reed: The boutique IRB size and specialization allows us to be more responsive and personal in our client interactions. Because we are smaller, we can offer more hospitality and better site relationships. Our competitive advantage is our ability to invest more in the vision and goals of our clients. Our target market is start-ups and small to mid-size pharmaceutical and biotechnology companies. Our therapeutic areas of specialization are oncology, cardiology, and neurology, but we have 15 years of experience reviewing most areas of Phase I–IV research.

Attracting our target market has been key to creating a positive work relationship, as well as to retaining sponsors for future work. In a highly competitive market, it is essential that we demonstrate a real understanding of our prospective clients’ needs and their pain points. While the two large private equity group–owned IRBs may dominate our industry by offering one-stop-shop services, a niche company like ours still has a place.

Principal IRB is a totally electronic IRB. Our digital platform, LAUNCH, is compliant with 21 CFR Part 11 of the *Code of Federal Regulations* and is a critical component in our strategy to

streamline the operations of our clinical study sites. We were set up to work electronically long before COVID-19, and that has been a huge asset to us as the industry shifts toward more virtual visits and trial design. This is a very unique part of our smaller IRB.

ACRP: Your company is female and minority owned. How does this impact your perspectives on the kinds of studies you are asked to review?

Hughes: Diversity is not only reflected in our ownership structure, but we also make sure that it is a part of the review committee composition. We believe that there is immense benefit in the collective experiences and opinions from a group that represents more than a single gender, race, and ethnicity. We see the importance of this time and time again when reviewing studies involving diverse research participant populations.

Reed: Principal IRB is a diverse workplace which pulls from a larger range of experiences and sources. Diversity brings new insights to problem solving. Diversity increases innovation, creativity, and strategic thinking, leading to improved results for our company.

ACRP: Can you share some quick details about how accreditation for IRBs works, and what advantages come from achieving accreditation the way you have?

Reed: The primary purpose of having accreditation through the Association for the Accreditation of Human Research Protection Programs (AAHRPP) is to strengthen protections for research participants. AAHRPP instills trust among research partners and sponsors. AAHRPP-accredited organizations often insist that accreditation status be a determining factor in decisions on external IRB review. Virtually all sponsors require all independent IRBs to be AAHRPP-accredited.

Becoming accredited was a rigorous, two-year process for Principal IRB, but it is the gold seal of approval in our industry. Accreditation signifies that we have built the necessary infrastructure for a quality human research protection program that reduces the risks of noncompliance. AAHRPP accreditation also enhances our standing with U.S. federal agencies, which are more likely to target non-accredited IRBs for inspections.

ACRP: What major trend or trends do you see shaping the world of IRBs as we head farther into the 2020s?

Hughes: In the age of COVID-19, we have seen an acceleration in telemedicine. Physical and mental health appointments are being conducted using video and wearable health technology. I think the future will bring an explosion in what I call teleresearch, with a rise in development of health device technology and clinical researchers normalizing remote assessment and monitoring. Principal IRB is prepared for this shift. The company has been virtual from the start. We embraced a fully electronic model in 2017, which is why we were able to continue without interruption during the spring shutdown and to accomplish full AAHRPP accreditation in September 2020.



Gary W. Cramer (gcramer@acrpnet.org) is Managing Editor for ACRP.

IRB INSIGHTS (PART 2)

Press Releases, Predictions, and a Canadian Perspective on Research Ethics

Erica Heath, CIP, MBA; Dorothy Herbert, BSc, MAppSoc; Gary W. Cramer



Conditions never seem to stand still very long these days in the world of institutional review boards (IRBs) and other formats of ethics review bodies for clinical trials. For example, WCG [announced in October](#) the unification of its five IRBs—Western IRB (WIRB), Copernicus Group IRB (CGIRB), Midlands IRB (MLIRB), New England IRB (NEIRB), and Aspire IRB—into the single WCG IRB brand. Donald A. Deieso, PhD, WCG CEO, termed it an “example of our commitment to positively transform the clinical trial process while keeping patient safety as our highest priority.”

Meanwhile in November, Advarra, a supplier of IRB and institutional biosafety committee (IBC) review solutions and clinical site technologies, [announced the acquisition](#) of Longboat, a provider of clinical trial technologies focused on site training, protocol compliance, and patient engagement. According to Gadi Saarony, CEO of Advarra, the acquisition “creates a natural bridge from our IRB and IBC reviews and consulting services to our existing site-facing technology solutions” to “provide comprehensive offerings to facilitate the clinical research journey, with sites and trial participants in mind.”

With such moving and shaking in the IRB environment as a background, this second part of *Clinical Researcher*’s “IRB Insights” for this issue welcomes the following commentaries from experts in ethics review with perspectives from the United States and Canada.

Gary W. Cramer (gcramer@acrpnet.org) is Managing Editor for ACRP.

Predictions to Consider for the Future of IRBs



Making predictions is always a tricky business, but since the subject is near and dear to me, here are my best guesses about where IRBs are going in the near future.

Single IRB (sIRB) of Record

The U.S. Food and Drug Administration (FDA) regulations require investigators to have IRB approval for studies, but the source of that IRB approval is left to the investigator and sponsor. As of the early 1980s, most sponsors recognized that it was most efficient to have one central IRB review with that IRB incorporating review of all investigators/sites. This worked nicely for sites with no internal board, but when the investigators were in an academic medical center (AMC), they were usually required to use their own institution's board. Eventually, like pulling teeth, one AMC after another started to accept the determinations of external boards.

Within the National Institutes of Health (NIH) there was a shift in 2017 that appeared to be sudden; multicenter grants would be required to name a single IRB to review for all the sites. This system is rapidly evolving, has now spread to grants from almost all federal agencies, and has proven to be anything but efficient. The minor problem is the actual IRB review. The major problem is the bureaucracy that surrounds institutions agreeing to rely on each other.

The Common Rule and institutional policies require a written reliance agreement between or among the institutions in order for one institution to rely upon the IRB in another institution. Academic institutions—most with “the very best IRB in the country”—were hesitant to defer to any other institution's IRB. With the mandate to rely, there has emerged a bureaucracy covering reliance agreements, “local conditions,” and the creation of consent documents acceptable to both reviewing IRBs and relying institutions.

There are several groups (e.g., [SMART IRB](#)) dedicated to negotiation of reliance agreements. Once the reliance agreement is signed, one IRB becomes the lead and the others rely on it. The

methods of communication, extent of review, individualization of consent and recruitment documents, and deference to “local” conditions are slowly becoming more mutually understood. Eventually, the single IRB of record (sIRB) system will be sorted out and may eventually become as efficient as the sponsor use of central IRBs, but it is likely that this will take several more years.

The sIRB movement is likely to cause a significant change to human subject protection in small hospitals. When review of clinical trials is outsourced, small hospital IRBs that used to meet monthly or quarterly often have no full board studies left. Even now, many small IRBs have no reason to meet although the size of their research portfolio remains as big as ever or even bigger. Management of this portfolio by a hospital research or compliance department will become more necessary than a functioning IRB. An IRB and IRB administrator may be retained for review of the remaining minimal risk studies, but their local expertise in IRB review of clinical studies will decline.

Growth of the External IRB Business

The first independent (or external) IRB is said to have been founded in 1968, although most were formed in the 1970s and new ones continue to emerge. As with internal IRBs, these external ones exist within a larger structure (the “institution”) that sets the tone and direction for the boards. The small-business, personal service nature of these companies continues in several remaining external IRBs, but as noted in the introduction, there are two very large companies owned by venture capital groups that also run a variety of clinical trial–related companies. The pros and cons of this can be debated, but these two companies certainly dominate the market.

In this environment, it is likely that external IRBs of all sizes will be increasingly selected as the reviewing sIRB of record for federally funded, multicenter clinical studies such that IRBs become even more centralized.

COVID-19 and IRB Review

The isolation requirements caused by COVID-19 have necessitated changes in the operations of both IRBs and sites. What might never have been considered possible a year ago has become

commonplace. IRBs are meeting remotely; plans for consent following phone, video, and Zoom discussions are approvable; waivers of signature are more common; and studies are approved for remote visits, use of remote monitoring devices, and follow-up visits. These changes have been thoroughly covered in other articles. The question is whether we can ever return to the “old normal” or if the COVID-19 changes have been so disruptive and illustrative that we will find we like the “new normal” and will never go back.

Dual Regulatory Systems—Is Harmonization in Our Future?

The more things change, the more they stay the same. In clinical research there have been two regulatory structures—one from the FDA (21 CFR 50/56 in the *Code of Federal Regulations*) and the other from the Common Rule (45 CFR 46). They describe the operations and requirements for IRBs in almost the same way. Other than that, they derive from different sources, use different definitions, address different issues, cover different populations, have very different enforcement, penalties, and guidance, and, although similar, are distinct in ways that only a small percentage of regulators really appreciate. This duality affects investigators subject to both regulations and is particularly evident in minimal-risk studies.

Over the years this dual system grew, sometimes harmonizing and sometimes not. With the 2018 iteration of the Common Rule, that rule changed but the FDA requirements did not. Although we expect eventual harmonization, at least in the near future it appears these two systems will remain quite separate. I do not envision this changing.

Who knows what the future will bring? These are some best guesses, but if this year has taught us anything it's that, well, anything is possible.

Erica Heath, CIP, worked at UCSF before founding an independent IRB, Independent Review Consulting (IRC), Inc., in 1984. In 2010, IRC and the Ethical Review Committee jointly formed Ethical and Independent Review Services (E&I Review). She has retired in the San Francisco Bay area.

A Canadian Perspective on the Mission of Research Ethics Boards

Here is some background and my opinion on the latest, greatest trends affecting how research ethics boards (REBs) that review clinical research in Canada function.

As I write this, our board, the REB for the Interior Health Authority in British Columbia, Canada, currently has 96 clinical studies active or under review (though a few have been suspended by the principal investigators due to COVID-19). That total includes 32 clinical trials, 10 biomedical research studies which are not clinical trials, and the remainder are other forms of clinical research (chart reviews, registries, etc.). Our REB also reviews social sciences research; clinical trials make up about 10% of all the research we review, so my perspective is from that somewhat limited basis.

For several years in British Columbia, REBs have been working together to create a platform for “harmonized” ethical review. This has substantially changed the landscape in the past two years or so, especially since we went live with the launch of a common electronic platform for REB applications involving two or more institutions in the province who entered into a partnership agreement (the partners are regional health authorities and academic institutions). Since the launch in January 2019, we have further refined the harmonized approach (a single REB application to gain ethical approval at all partner institutions) to achieve greater streamlining in special cases, including review of cancer research and review of COVID-19 research. For more information about the Provincial Research Ethics Platform (PREP) and harmonized ethical review in British Columbia, please visit <https://researchethicsbc.ca/> or contact Terri Fleming, Director of Research Ethics BC, at tfleming@bcahsn.ca.

For cancer research, we have a single specialized board at BC Cancer, the institution that treats cancer patients throughout our province. If cancer research is happening locally, at a site where my REB would otherwise have geographical jurisdiction, it is still reviewed by the one expert board. We accept its review and approval.

There is a movement in Canada to do something similar (i.e., have a single expert board) for review of pediatric research. Information is available at <https://cheerchildhealth.ca/>.

The other latest, greatest trend is the “rapid ethical review” process for COVID-19 clinical studies adopted by the boards that participate in the harmonized ethical review process. To put this in context, ordinarily institutional REBs require (on average) two to three weeks of lead time for members to review a clinical study in advance of a full board meeting. This is primarily because our clinical reviewers are also busy clinicians.

When it came to the pandemic though, a province-wide commitment was made to review COVID-19 clinical studies within five days of receipt. This is an incredibly compressed time frame, especially as REB members were and are also dealing with extraordinary changes in their work environments and likely their home environments. It was a privilege to see them rise to the challenge.

Dorothy Herbert, BSc, MAppSoc, is Research Ethics Board Coordinator with the Interior Health Authority of British Columbia, Canada.

PRESCRIPTIONS FOR BUSINESS

Negative Shocks May Hit Twice in Pharmaceutical Development

Manuel Hermosilla



One defining aspect of the pharmaceutical industry is its high exposure to negative shocks—product recalls, tornados that shut down production lines, Phase III failures, you name it. As my thinking about some of these shocks has grown over time, I’ve come to realize some shocks may hit twice—the second time being the moment a sub-par decision is made in an attempt to recover from the original hit. With stakes being so high, it seems particularly important for leaders in this industry to remain aware that they are not immune to the perils of *reactive* decision making.

This point can be underlined using a case study from my [recent research published in the INFORMS journal *Management Science*](#). The bottom-line message is that, in addition to requiring the self-awareness and reflectiveness of individual decision makers, preventing costly reactive behavior may require organization-level action.

The case study focuses on drug candidate in-licensing, which I’ll address from the perspective of a “buying” large pharmaceutical firm and refer to simply as “licensing.” Recent statistics suggest that more than a third of the new drugs launched by large pharmaceutical firms are obtained via licensing, often from a young and small biotech startup. This underrepresents the importance of licensed drugs because they tend to be more therapeutically and commercially impactful than those developed in-house by large firms.

Thus, it seems safe to say that licensing is a highly important activity for the modern pharmaceutical industry. Accordingly, these firms do not spare efforts to get the most out of it—in a typical year, a big pharma firm may identify and review several thousand licensing leads while following through only in a handful of cases.

The low ratio of completed deals to leads reflects a crucial aspect of licensing. Firms need to make sure they are licensing the “right” technology (i.e., one which they have the expertise to develop and that fits the firm’s portfolio and medium-term strategy). Much of the complexity of doing this has to do with the technological novelty of licensed drugs, most of which are unvalidated at the time of licensing, and about which the selling firm knows a lot more than any other scientific team in the world.

To deal with these complexities, large pharmaceutical firms employ multi-disciplinary teams through the scouting and screening process; but that’s not all. While the overarching goal of licensing is clear (developing a new drug), the specific hurdles that will appear along the way are highly uncertain and contracting parties may have different hierarchies for what is most important to accomplish (e.g., should the molecule be optimized for emphasized safety or efficacy? How soon should findings be published in an academic journal?).

The question for the buying firm then becomes, how to keep the selling party engaged throughout the (typically long) process? These considerations explain why reaching agreements is such a highly involved process, which usually takes the better part of a year or longer.

Picking Up the Pieces of a Phase III Failure

My analysis focused on the licensing behavior (and the fate of licensed drugs) in the aftermath of a distinctive kind of large, negative shock in the industry—the Phase III failure. Phase III trials are the largest, longest, and most expensive stage of drug development—the monumental last hurdle to overcome to reach the market. Unfortunately, experimental drugs fail to produce satisfactory results at this stage—as many as 50% by some estimates.

When these failures occur, organization-wide anxiety levels go up automatically. They mean that the years-long, collective work of many professionals in the organization will not pay off.

Perhaps more importantly, Phase III failures raise questions about the future (e.g., what product will fill the pipeline gap left by the failed drug?). Phase III failures are a true test of an organization's character—a time when measured, level-headed decisions are particularly important.

I studied the problem by constructing a sample that covered the licensing and development activity of 20 of the largest pharmaceutical firms worldwide between 2000 and 2015. The sample contained about 400 Phase III failures, scattered across therapeutic areas, firms, and time. Even though these failures are not completely random events (e.g., they are more common in cancer), there is a lot of randomness relative to the specific time at which they occur.

This was an important observation for my first analysis, where I looked at how much licensing there is in the immediate aftermath of a Phase III failure. Because the precise timing of failures is given by factors that are close to random in practice (e.g., patient recruitment, the molecule's specific therapeutic properties), these events could be seen as natural experiments. I found that, in the year that follows a Phase III failure, licensing activity about doubles; firms seem to react to failures.

In general, does this type of reaction ultimately help the firm overcome the adversity or only further aggravate it? To answer this question, I followed the development histories of all licensed candidates, separating them into those licensed “in a rush” (within a year of a Phase III failure) and those licensed under normal conditions. The former group was significantly less likely (about 10% less) to reach the market than the latter group. This result portrays rushed post-Phase III failure licensing as self-added insult to injury.

Some evidence indicates that contracting issues may be to blame for this outcome—rushed negotiations that lead to contractual “loose ends,” which increase the chances of inter-organizational frictions and, ultimately, derailed collaborations. Insufficient or weakened due diligence standards may also be relevant.

Conclusion

[Leading industry figures have suggested](#) that the industry's current productivity struggles may not just be a matter of the underlying science—decisions and personal accountability may also play a role. This argument resonates loudly in the present context—because success is so elusive (i.e., most drugs fail the process), the incentives faced by research and development leaders lead them to prize activity (number of deals, pipeline size, new trials) rather than accomplishment. As illustrated by this case study, this scenario could be a fertile ground for decisions that may end up being damaging overall, if there is no system of checks-and-balances in place.



Manuel Hermosilla is an assistant professor in the CareyBusiness School at Johns Hopkins University, where he studies diverse aspects of new product innovation, with a focus on the biopharmaceutical industry. He is an active member of the Institute for Operations Research and the Management Sciences (INFORMS).

Clinical Research Saved My Life, Now it is Time to Make it Better

Al O. Pacino



Over the course of my life, I have overcome several life-altering challenges. My experiences have uniquely shaped me, and they have ultimately led me into a place within the clinical research community. It is imperative that future generations have access to a more sustainable and innovative clinical research ecosystem so that more lives can be saved, like mine. By acknowledging the current realities of clinical research, upcoming professionals will be able to identify roles

for themselves as well as provide solutions.

Fifteen years ago, my life was saved by the healthcare and clinical trial ecosystem. I was a head and neck cancer patient, and the drug solution (along with extensive radiation) ultimately sent my cancer into remission. However, not everybody in the world has the same opportunity I did. From then on, I felt it was imperative to develop a global system where everybody would have the same opportunity to access the benefits of a new healthcare and clinical research ecosystem. All these years later, I am still committed to the challenge of improving quality of life around the world through entrepreneurship, patient advocacy, and philanthropy.

My time in the industry, as well as being a cancer patient, has made me see up close where the system could change by educating the culture and incentivizing the establishment to modernize our industry. Clinical researchers and healthcare professionals have the opportunity to positively affect the patient experience in many ways. This is more achievable when institutions such as sites and sponsors are committed to maintaining patient privacy and to complying with global regulatory standards.

The goal is to improve human subject protection and patient safety by developing globally accepted standards of care. With more connective solutions on the rise, staff and management can implement new protocols for systems to expedite study start-up and closeout. By adapting to changing regulatory expectations of clinical research, sites have a higher chance of gaining studies and achieving long-term sustainability.

Lessons Going Forward: Privacy and Compliance

A helpful tip for future clinical research professionals is making sure that the records for all your required and independently gained professional trainings and other education, networking, and service experiences are up to date and secured at all times. Stay aware of any important regulatory updates or laws that may impact your research-ready status. For example, the General Data Privacy Regulation (GDPR) which was implemented May 25, 2018, protects professionals and empowers ownership over their own data and personal information. In the U.S., the California Consumer Protection Act (CCPA) implemented January 1, 2020, Nevada's first data privacy legislation and multiple other states are expected to follow with implementation very soon.

By properly educating our culture and understanding what is being legally required of all stakeholders, everyone in the ecosystem will benefit, including patients, in the long run.

Finding Your Place and Making a Difference

Since clinical research is an international endeavor, several major institutional pillars support the industry to make sure it runs safely and efficiently. Sponsors, contract research organizations, research sites, hospitals, universities, and tech companies provide necessary functions to provide innovative outcomes. This means that there are several points-of-entry available for healthcare professionals to improve the greater ecosystem.

Instead of viewing the current system as “overwhelming” or “too bureaucratic,” aspiring clinical research professionals should see an opportunity to provide their advanced skill set to re-shaping

the direction of future health outcomes and the protection of all patients. Streamlined communication between your organization's departments should provide increased productivity and shared responsibility. When a more collaborative mindset and infrastructure are fully realized, we can begin to see more harmonious developments for all.

Conclusion

As specialized professional members in the clinical research process, we should help each other to modernize the healthcare and clinical research ecosystem together. Our world is rapidly evolving, and it is important to keep up. There should be a collaborative commitment to all patients equally, regardless of race, religion, socioeconomic status, political affiliation, or geographical area. We should be excited by the enthusiasm from global establishments and institutions which are now aligning their business models with an effort to benefit all lives through sustainable innovation. Individuals interested in the clinical research industry should ask themselves how they can help in the ecosystem to “leave no patient behind.”



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

SITES & SPONSORS

The Future of Clinical Trials Will Require a Focus on the “Long Tail”

Kourosh Davarpanah, MS



Traditionally, the clinical trial industry has long followed [the Pareto principle](#) (or 80/20 rule), in which clinical research has relied heavily on a finite number of large sites to provide the vast majority of patients. With [5% of sites running 70% of trials](#), only a small percentage of patients with privileged access to these sites have had the opportunity to participate.

At the same time, there has never been more trial opportunities for patients: Key therapeutic areas such as oncology and immunology are experiencing unprecedented innovation, with late-stage oncology trial pipelines increasing 77% since 2008. Still, 85% of trials fail to retain enough patients. On top of this, the coronavirus pandemic is upending the logistics of recruiting and engaging with patients, who are less willing and able to travel long distances to participate in trials.

We are fast approaching a supply-demand issue that will have significant, long-term impact on trial delays and costs—and ultimately further impact patients. Addressing increasing competition and decreasing patient participation will require a reimagining of the way sites and sponsors collaborate on clinical trials.

Focusing on the Long Tail

Traditionally with inventory management, suppliers have focused on the 20% of products that contribute to 80% of their revenue. However, this limits choice and access, while significantly driving up competition.

In the last 20 years, the concept of an online “marketplace” has emerged to transform and resolve similar supply-demand issues in multiple industries. Whether it’s providers of e-commerce (such as Amazon), vacation rentals (such as AirBnB), or regulated industries like insurance and mortgage services, many sectors have found success leveraging a marketplace model to bridge the gap between supply and demand.

The reason that marketplaces work is they allow the end user to explore the potential of the other 80% of products: the “long tail.” Established in 2004, [the long tail](#) concept theorizes that the future of business is selling less of more in order to eliminate the bottlenecks between supply and demand. Rather than focusing on a few key offerings, this new economics of distribution allows suppliers to turn their focus to the many more products throughout the “tail,” which can collectively create a new market as big as the one we already know. At the same time, as you go farther down the tail, the less competition you have.

By adapting this approach to clinical research, sponsors can select sites with specific attributes (access to diverse or research-naïve patients, low competition) that make them a great fit for their study while making it easier for community sites to offer the trials for their patients.

A New Model for Sponsor-Site Collaboration

To overcome current clinical trial challenges and ensure the industry's efficacy in the future, we need to apply the same long tail concept to the sponsor-site collaboration model.

Many community sites have extensive research experience, tight-knit relationships with their community, low competition, and the desire to offer more care options to their patients.

However, limitations of the current collaboration model inadvertently prevent sponsors from broadening access to many such sites. Community sites struggle to showcase their strengths and

get on sponsors' radars, while sponsors are actively trying to decrease costs by reducing the number of sites selected per trial.

A marketplace enables us to refocus on the long tail of underutilized sites by:

1. Empowering sponsors to discover—in an efficient and cost-effective manner—the hundreds of community sites that have strong enrollment potential and the right clinical research experience to deliver on their commitments.
2. Equipping sites to successfully market their capabilities and reach a wider audience.
3. Encouraging organic growth in site activities and patient referrals.
4. Centralizing and streamlining processes between sponsors and sites to reverse the challenging economics of clinical trials.

At the same time, a marketplace can also empower sponsors to quickly identify the right balance between large academic research sites and untapped community sites to meet trial requirements. Similar to how an e-commerce marketplace provides a balance between large marquee products and niche offerings, a clinical trial marketplace can provide the greatest visibility to match the right sites to the right trial and ultimately broaden access to patients.

Ultimately, focusing on the long tail allows us to reimagine the sponsor-site collaboration model, providing increased opportunities to bring clinical research to each and every patient regardless of who they are and where they live.



Kourosh Davarpanah, MS, is Cofounder and CEO of [Inato](#), which helps biopharmaceutical companies and contract research organizations match studies to sites, and helps sites increase their patient pools.

Five Ways Clinical Trials Will be Transformed in 2021

Alison Holland; Jena Daniels; Rasmus Hogleffe; Ingrid Oakley-Girvan, PhD, MPH;
Dr. Michelle Longmire



If 2019 was the year of personalized medicine, 2020 was the year of decentralized trials. Ready or not, the COVID-19 pandemic ushered in a new era of clinical research—the advantages of which are only just beginning to blossom. Beginning this year, the life sciences industry will see new virtual trial designs adopted by a much larger, broader section of sponsors, sites, and patients. As a result, expect great strides forward in trial access and participation, the growth of real-world evidence to enable better outcomes, and huge leaps in trial efficiency and speed. In this column, Medable experts share their predictions on changes that will shape the clinical environment in 2021.

The Flexibility of Decentralized Trials Will Drive Widespread Adoption

Alison Holland, Head of Decentralized Trials

The promised decentralized trial (DCT) revolution has gained traction in 2020, but we have significant progress yet to achieve, even as we see bolder commitments to this more patient-centric, more efficient model today. Industrywide, the decentralized approach to clinical trials has been philosophically embraced for its advantages, but physically adopting and operationalizing the model—particularly mid-flight on studies—require a commitment to overcoming fear of change. The model’s inherent flexibility will be instrumental to calming any concerns and will drive widespread adoption through 2021.

DCTs are each unique by design, and not one-size-fits-all. In contrast to the rigidity of traditional randomized control trials, DCTs offer a modular framework, affording choice to sponsors, sites, and patients. All stakeholders will become accustomed to having options. At that point, DCTs

will no longer be a “nice to have,” but an expectation if not a stipulation of all protocols in the future. Just as we all appreciate and expect a personalized engagement in consumer activities—think online retail platforms such as Amazon—physicians, patients, and site teams should expect configurable and personal options for engagement that replicate consumer experience standards.

By the end of 2021, we will come to a tipping point where patients recognize how much less burdensome it is to participate in DCTs, sites recognize how technology enables rather than hinders such trials, and everyone appreciates how many ways sites and sponsors can save with this approach. The freedom to create trial designs that work best for each site, each patient, each protocol will be too great of a siren song—and will make DCTs easily scalable. The industry will not revert to the disjointed, manual, pre-COVID-19 way of conducting trials as progress so often requires abandoning long-standing behaviors to embrace the new.

Virtual Tools Will Expand Patient Access to Clinical Trials Tenfold

Jena Daniels, Director of Research and Head of Medable Patient Advocacy Council

Historically, access to clinical trials has been one of the greatest hindrances to study speed and success. By the end of 2021, many more pharmaceutical companies will leverage a DCT model, which will not only open doors to more patients but also reduce racial disparity in healthcare and improve overall outcomes.

Across the U.S., there is tacit acknowledgement of a two-tier system—those who have access to quality healthcare and those who do not. The difference between the two often tips the scales in terms of population representation in trials. DCTs improve access by bringing the trial to the patient, removing the burdens of travel and distance to make trials feasible across demographics. DCTs can also capture real-world data from patients “in the moment,” dramatically improving the quality of information.

This is not theoretical. The National Center for Biotechnology Information found that a DCT model recruited three times as many patients three times faster than the traditional model. The patients in the decentralized model also better represented urban and rural areas. These benefits

are particularly important for rare diseases, as trials are few and far between and patients may be spread across wide geographic areas.

Also, expect to see diversity increasingly baked into study protocol design and early product development. This will extend beyond people of color to include different genders and ages. We will see patients from all backgrounds involved in the study process from the start. As an example, Medable's Patient Advocacy Council (PAC) has patients ranging in age from 20 to their mid-70s, a mix of female and male members, and will expand its racial diversity in early 2021. The PAC informs Medable products and trial design—not on the back end, but at the beginning when they can make the biggest impact.

Improvements to Patient Care Will Trump Fear of the Unknown for Research Sites

Rasmus Högrefte, Vice President of Decentralized Trial Innovation

The COVID-19 pandemic turbo-charged the use of virtual tools and a decentralized model for clinical research, but as life resumes more normalcy, the pharmaceuticals industry will continue its pace of adoption of DCTs. Investigator sites, which have been stuck between the “fear of missing out” and fear of the unknown, will cautiously push forward with DCTs as they see patients receiving better care.

It will not happen overnight, but sites will slowly have less trepidation as they see the impact that a decentralized approach has on patient care. DCTs allow patients to stay safely in their homes and still have physician-monitored access to potentially life-altering new therapies. Further, because patient health is surveilled continuously using wearables, electronic diaries, virtual check-ins, and other tools, they receive premier care. Sites can respond in real time and engage directly with patients more often.

Real-world data from in-the-moment patient accounts (before memory-muddled experiences are recounted at the next in-person visit weeks later) will also improve data quality and could lead to better outcomes. With greater trial access across all demographics, study data will be more comprehensive for greater insight into developing new treatments. The improvements in trial speed will drive more novel drugs to patients faster and for less cost.

DCT adoption will steadily increase through 2021 as improvements in patient care, data quality, and trial outcomes assure sites, sponsors, regulators, and patients that there is nothing to fear.

Digital Biomarkers Will Expose “Simmering” Symptoms Before They Turn Serious

Ingrid Oakley-Girvan, PhD, MPH, Senior Vice President of Research and Strategy

Tech-minded epidemiologists are working to crack the code of digital biomarkers as they could signal early and important changes in the trajectory of a disease. Researchers are now able to capture quality data, on a longitudinal scale, and harness the data across groups of patients to establish accurate markers. The fallout of COVID-19 has accelerated this effort as more companies take a decentralized approach to clinical trials and leverage remote data capture.

While the ability to capture digital biomarkers remotely is often constrained by cost and logistics, there are rich data that can be collected reliably with modern technology. For instance, a daily video that shows progressive changes to a Parkinson’s patient’s shuffle, a wearable device that measures hand tremors continuously, and a digital sleep monitor that tracks REM sleep cycles all inject new factors into the research equation to help determine accurate digital signatures. Just as critical, DCT platforms enable researchers to collect higher quality data from patients in their natural environment when they are most relaxed, eliminating the “white coat effect.”

As DCT adoption increases, science will be able to identify the early, “simmering” symptoms that could turn into adverse events later in the trial. Since the development of symptoms has the potential to jeopardize patient safety and instill fear and panic, patients could drop out of a trial prematurely. Identify these early, however, and the care team may be able to mitigate symptoms, prevent psychological harm, and avoid losing patient participation—especially if the incident was not caused by the investigative drug but by external factors, such as dehydration or lack of sleep.

In 2021, the momentum of DCTs and virtual technologies will allow clinicians and researchers to better identify digital biomarkers to help improve care and maintain the integrity of vital

clinical trials. It will be the beginning of truly proactive patient care that is mindful of individual situations—the ultimate in long-promised personalized medicine and patient centricity.

Greater Access Will Drive Radical Improvements in Trial Efficiency and Effectiveness

Dr. Michelle Longmire, CEO and Cofounder of Medable

When I was a child, my father sought to rein in my gusto by saying “don’t put the cart before the horse.” So, when we founded this company and developed an early vision for DCTs, I resolved to curb my enthusiasm about the potential for this novel approach. Now, as an unimagined consequence of the pandemic, we are starting to see the impact that decentralization will have on trials—making them both more efficient and effective.

This past year, the decentralized model provided a vital stopgap to overcome the halt of clinical trials for thousands of shut-in patients and trial staff. What served as a band-aid in the short term quickly developed into a recognition that decentralized approaches can deliver a variety of benefits to sponsors, contract research organizations, sites, and patients. We saw faster enrollments and greater retention for patients participating from home. We saw more, and higher quality, real-world data. We saw more efficient processes and a dramatically improved patient experiences. We saw the resistance to digital and mobile technologies melt away, as televisits and remote screening and enrollment made participation easier for more patients from more places.

As the life sciences industry continues to march forward with its adoption of a decentralized model, it is incumbent upon technology providers like us to continue evolving our platform and solutions for even greater benefit. Companies simply will not go back to pre-pandemic ways. We will all continue to learn and innovate, and the domino effect will drive 50% to 70% increases in trial access and efficiency overall—ultimately leading to more effective therapies for more people around the world.

[Medable](#), headquartered in Palo Alto, Calif., is on a mission to get effective therapies to patients faster by transforming clinical drug development with disruptive technologies for connecting patients, sites, and clinical trial teams to improve patient access, experience, and outcomes.