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Clinical Researcher

The Authority in Ethical, Responsible Clinical Research

December 2021 (Volume 35, Issue 9)

Parts of a Whole: Evaluating and Elevating Your Role in the Clinical Research Enterprise

Clinical Researcher

Association of Clinical Research Professionals

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Credit-granting Home Study tests are available at https://www.acrpnet.org/home-study/, along with downloadable PDFs of the relevant articles and questions. The test from this issue should be online in January 2022.

Six issues of *Clinical Researcher* will be published on a bimonthly schedule in 2022, starting in February. The Home Study tests will grant 3 Continuing Education Credits.

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EXECUTIVE DIRECTOR'S MESSAGE

I'm Grateful for You—and My Gratitude Gurus

Susan P. Landis, Executive Director of ACRP

Here's something you don't know about me: I follow social media accounts that every so often tell me how great I am. At the end of a hard day when I'm scrolling through Instagram, @thrive might tell me, "You got this!" @BreneBrown will remind me to take a breath, and Kamau Bell's mom, @jcheathambell, keeps me on track with strong statements from Black leaders that empower.

Why does this matter to you? Because if you haven't heard it lately—you're amazing. What you are doing to advance medicines through helping to lead clinical trials and studies makes a world of difference. Actually, you make a different world. At the end of the year, when we're stretched thin, when we have multiple lists occupying our brains and deadlines that seem impossible to meet, you might need someone to say, "You are enough," like a recent message on @unwomen told me.

During this season of gratitude, ACRP wants to make sure that your contributions to clinical research are acknowledged. We're grateful for all that you do. We see you. Thank you.

We hope that you carry our gratitude with you throughout this season and into the New Year, especially. We're making our 2022 to-do lists and checking them twice to deliver new things for you, including a learning-packed annual conference in Orlando next spring, new training and development programs, and a new toolkit to encourage interest and promote diversity in our clinical research workforce.

Further, as you *wrap* things up for this year, we checked one thing off your list—pulling together a meaningful holiday music playlist to stream when the mood strikes. The ACRP Holiday Mix is a handcrafted and algorithm-free selection of seasonal tunes, offered from us to you.

Happy holidays from everyone at ACRP! Thank you for supporting our mission to promote excellence in clinical research.

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CHAIR'S MESSAGE

From Guinea Pigs to Heroes

Erika Stevens, MA, FACRP, 2021 Chair of the Association Board of Trustees for ACRP

Is the perception of clinical research different today than it has been historically?

In just under 20 years, the public's view of clinical trials has evolved from something akin to a taboo subject to something much closer to sentiments we can all be proud of—though full recognition of how everyday citizens are key to medical breakthroughs has yet to be achieved.

In 2002, the cover of an issue of *Time* magazine showed a make-believe scenario of a woman inside a cage, with the title "Medical Testing" and claims of researchers turning millions into guinea pigs.{1} The article asserted that people who participate in clinical trials do so out of desperation, questioned the safety of medical experiments, and warned against the risks of clinical research.{2}

That was then, this is now. The cover of the December 13, 2021 issue of *Time* features the scientists responsible for mRNA (developed into the vaccine to thwart COVID-19) as "2021 Heroes."{3} However, where is the recognition of the thousands of volunteer research participants? Where is the recognition of the clinical research workforce involved in the conduct of managing clinical trials in the middle of a global pandemic?

More than 40,000 people in the U.S. participated in clinical trials in 2015.{4} Between 2015 and 2019, U.S. participants represented 35% of overall global clinical trial participation.{5} A sharp increase in clinical research participation is demonstrated with the development of the COVID-19 vaccine. Pfizer reported more than 43,000 participants{6} and Moderna reported 30,000 participants{7} in their respective Phase III clinical trials. The increase in public awareness of

clinical research and the outcomes resulting from trials are tantamount to a sea change for the enterprise.

Internet searches for the word "vaccine" were up more than 600% from 2019 to 2020 and more than 1,000% from 2019 to 2021.{8} As a result, Webster's named "vaccine" the word of the year for 2021.{9} Even still, the recognition of the workforce supporting the development of recent vaccines is absent.

ACRP's educational efforts with lawmakers—to advance clinical trials nationally—remain a top initiative for your Association. Along with our advocates, ACRP continues to promote excellence in clinical research education and to garner long overdue professional recognition for those doing the vital work in sponsor, site, academic, nonprofit, and vendor settings.

On behalf of ACRP, thank you for efforts in advancing vaccines and improving health outcomes. It was my privilege to help lead this organization and to serve as Chair of the Association Board of Trustees in 2021.

I wish you all the best jusqu'a ce qu'on se revoie (until we meet again),

References

1. http://content.time.com/time/covers/0,16641,20020422,00.html
2. http://content.time.com/time/subscriber/article/0,33009,1002263,00.html
3. https://time.com/heroes-of-the-year-2021-vaccine-scientists/
4. https://www.fda.gov/media/106725/download
5. https://www.fda.gov/media/143592/download
6. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-conclude-phase-3-study-covid-19-vaccine
7. https://clinicaltrials.gov/ct2/show/NCT04470427
8. https://amp.cnn.com/cnn/2021/11/29/us/vaccine-merriam-webster-2021-word-of-the-year-trnd/index.html
9. https://www.merriam-webster.com/words-at-play/word-of-the-year/vaccine

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PEER REVIEWED

Investigator Compensation: No One Size Fits All

Suzanne J. Rose, MS, PhD, CCRC, FACRP

Managing investigator payments is probably one of the most challenging aspects of conducting a clinical trial, but it seems that it is the best kept secret in our industry. It is the topic that generates the most interest when discussed with colleagues, but unlike other straightforward processes in our industry, the topic of investigator compensation is one that has guidelines but no specific steadfast rules to let us know if we are compensating appropriately or inappropriately. While there are several models that are discussed in the literature,{1–4} there is no clear consensus on which model is the best fit for each site.

The first stop in de-mystifying the conversation on investigator compensation is to identify and explain key operational and compliance factors for consideration, such as fair market value (FMV) and equity across specialties. Does one or can one size fit all? How much should we pay investigators for their work on a clinical trial and what laws govern investigator compensation so that we remain compliant? While it is important to understand the Stark Law and the Anti-Kickback Statue, and the exceptions and Safe Harbor that allow physician payments, these are excellently described elsewhere.{2}

We will therefore focus on FMV because amounts paid to investigators are considered part of their overall compensation amount and therefore subject to the FMV Guidelines. Importantly, both FMV and commercial reasonableness are important concepts in the Anti-Kickback Statute Safe Harbors and Stark exceptions.{2} In addition, as most principal investigators (PIs) are physicians, the American Medical Association (AMA) provides clear guidelines on managing

conflicts of interest in the conduct of clinical trials, in that financial compensation should be at FMV and the rate of compensation per research participant should not change pursuant to the number of subjects enrolled by the physician.{5} Thus, the rate of payment for professional services should remain constant irrespective of the PI's success enrolling or completing study subjects compared to their target.

Background

The concept of FMV extends back 120 years{6} and is described in the *Code of Federal Regulations* as "the price at which the property would change hands between a willing buyer and a willing seller, neither being under any compulsion to buy or to sell and both having reasonable knowledge of relevant facts."{7} The Centers for Medicare and Medicare Services (CMS) defines market value as "the value in arm's length transactions, consistent with the price an asset would bring as the result of bona fide bargaining between well-informed buyers and sellers who are not otherwise in a position to generate business for the other party."{8} In 2003, FMV for research studies was first included in the Office of Inspector General (OIG) regulations stating "Payments for Research Services should be fair market value for legitimate, reasonable and necessary services."{9}

However, even with the clear instructions above, the rules do not provide advice on determining the FMV, which puts sites at risk. If the investigator is paid above FMV, it can give the appearance that it would influence his or her decision to participate in the trial or to influence the outcome of the trial, thus placing the institution at risk from legal and regulatory perspectives. If PIs are paid below FMV, they may not be willing to participate fully or enroll research participants, which could impact relationships between sites and sponsors. At the end of the day, there is no perfect percentile that exists for FMV calculation, as FMV for an investigator truly depends on medical specialty, geography, and physician experience.{10}

However, the following are helpful hints for a site to stay in line with FMV:

- Determine a pricing strategy with the billing team: Engage the billing team as partners in the pricing strategy. An important goal of any research study should be to properly compensate the hospital or private site for investigator time.

- Update the fee schedules on a yearly basis: Variations in compensation rates should be monitored closely on an annual basis to ensure FMV is appropriate by region and specialty.
- Provide full justifications for all fees charged in a clinical trials budget: The budget negotiation should not be a guessing game or contentious. Clearly outline all fees and justifications therein. Provide justifications up front, not when asked for them.
- Engage internal support or external vendor to create research and/or administrative hourly compensation fee schedules: There are several firms that can assist in developing your organization's internal compensation reference materials to be used in establishing the framework and market data consistent with your compensation philosophy related to physician research and/or administrative work effort. These firms can provide FMV payment (hourly rate) range recommendations for various physician specialties providing research and/or administrative services.

Finally, best practice is to create a FMV policy in writing to defend your site's actions and to prove transparency. In addition, please remember that a physician's "going rate" or past compensation does not necessarily constitute FMV; further, the values for administrative services most likely differ from those for clinical services. Therefore, it is important to engage a third-party vendor to clearly differentiate between research and/or administrative services.

PI Compensation Structure

Investigators can contribute to study in many ways,{1} and therefore the compensation should be fair, motivational, affordable, practical, legal, and agreeable.{3,4} To structure the investigator compensation model, we should include considerations for (clinical) relative value unit (RVU)–based services vs. administrative work in these models.

Relative Value Units (RVUs)

RVUs are measures constructed by Medicare to estimate productivity by calculating the relative level of physician time, skill, and expertise. Medicare relies on these measures to establish payment levels for physicians' services which are then described by Current Procedural Terminology (CPT) codes. This compensation model is typical when a hospital also employs physician-investigators as clinicians, and they earn RVU credits when they perform clinical services with CPT codes that are part of the clinical trial.

It is helpful to utilize different terminology when incorporating research RVUs into an existing electronic medical record. To this end, we have established "research RVUs," which are calculated per hospital policy as 1.5 times the Medicare rate across all specialties with one average RVU per visit type. At the end of the day, all RVUs end up in one bucket and look like regular RVUs. This way, regular patient visits are not seen as competition with research and the physicians are motivated to perform research in an existing RVU model.

When incorporating an RVU model into your investigator compensation program, it is important to remember that the model needs to account for research time with no corresponding CPT code. In addition, for study-specific oversight and research fees without CPT codes, the investigator cannot receive RVU credit and is paid according to FMV, as discussed previously.{2}

Compensation Models (External to RVUs)

Fixed Fee or Percentage: The site pays investigators a fixed fee or percentage for studies, regardless of their contributions. These options are simple to manage but difficult to assess if they accurately reflect the FMV of the investigators' services.

Research Salary: At research sites where the investigators are employed by the site, investigators are paid a fixed salary for all their time spent working on clinical trials and all parties know the exact amount that will always be paid.

Hourly Wage: The site can compensate the investigator specialty-specific hourly rates for tracked time on a specific study along with activity performed. This can be seen as additional work by the investigator, who may balk at extra time spent on tracking their hours.

Fee for Service: The site compensates the investigator for specific services performed or time spent. This option is more time-consuming to administer, but strongly motivates investigators to perform the services they are contracted for.

Sub-Investigators: While the role of investigator is usually limited to a licensed physician, the sub-investigator role can be much more inclusive to include mid-level providers, such as physician assistants, nurse practitioners, and, at academic medical centers, residents and fellows.

They play various roles in a study and are often essential for success of the trial. Fee for service typically works well for sub-investigators and can be tracked inside the budget, via a spreadsheet or clinical trial management system. It is important to understand any sub-investigator's current payment structures inside the site or healthcare system and work with administration to ensure that salaried positions are capable of being compensated above and beyond their current salary structure, as well as being compensated for RVUs similar to their physician counterpart. At academic medical centers, payments to residents and fellows outside their salary will need to be carefully discussed and negotiated with the Graduate Medical Education Office and adhere to AMA guidelines.

Hybrid Model: In this model, a variety of the above options can be utilized. Fixed fees could be utilized for costs that are consistent from study to study, such as site initiation or monitoring visits. Fee for service would then be utilized for study procedures because they would be variable from visit to visit and study to study. An agreed-to administrative fee (in line with FMV) per visit type can also be included in this model along with research RVUs. The investigator then understands that compensation will be adjusted from study to study. This system is consistent with the financial success of the study while remaining within the regulatory guidelines.

Special considerations for all models:

- If the investigator is billing a third party/subject for routine services that are in the protocol, the site cannot also compensate for those services, meaning the physician or site cannot get paid twice.
- Ensure all investigators' work and time efforts are documented clearly.
- Written contracts and expectations are vital and should follow the guidelines set forth in The Personal Services and Management Contracts Safe Harbor or The Personal Service Exception.{2}

Regardless of the compensation structure, at the end of the day, it is important to remember that according to the tenets set forth by the International Council for Harmonization's Good Clinical Practice guidelines and the U.S. Food and Drug Administration, bonuses, finder's fees, or pay-for-performance to PIs based on the number of participants enrolled in or completing the trial are completely unacceptable.{11}

Compensation Models for Different Types of Physicians: Private vs. Hospital Based

Hospital and Medical Group Physicians

When working with physicians inside our system, the use of the centralized research office is required. We provide a consistent process to all studies so that all budgeting, contracting, regulatory approvals, and staffing issues are covered from study start-up to close-out to provide a concerted approach. All research funds are routed directly to the centralized research office with quarterly reimbursement made to research partnering physicians. We draft a master agreement with each physician and then utilize sub-orders to outline each study reimbursement and what payment schedule will be. The compensation follows a hybrid model approach including fixed fees, fee-for-service, RVU considerations, and administrative oversite fees.

We do have physician groups that request the money be distributed evenly across investigators or returned to their departments. Alternately, in departments where the studies might be supported by only one or two investigators, they opt to be paid individually. We always have these discussions up front, so they understand the options available to them. This model allows great flexibility amongst our physician groups, and they are able to feel engaged in the conversation from start to finish.

Private Physicians

When working with private physicians, understand that they have the desire to keep their patient population yet also are aware of competitive study enrollment. Private PIs can use their own clinical research staff (if they have them) or utilize our site staff if they lack adequate study support. In this scenario, a master agreement is drafted with each private physician group and then sub-orders are utilized to outline each study reimbursement and what the payment schedule will be. Compensation is provided for specific services performed by private physicians and their research staff following a fee-for-service model.

When we work with private PIs who provide all the staffing for studies yet require the use of the physical hospital space, we draft a facility use agreement where we can charge for management

of study drug, supplies, equipment, and oversite of any research billing that may occur. Some physicians find us so helpful to work with that they have stopped performing research procedures at other hospitals, which brings in revenue for the hospital and procedures we might not have captured previously.

Conclusion

Investigator compensation is not a one-size-fits-all model. It includes an open and honest discussion with the investigator in addition to adhering to FMV and staying within ethical guidelines. Investigators should be motivated, but not incentivized, to perform clinical trials and view this engagement as a partnership to enhance research efforts to better the lives of our patients.

References

1. Bowler A. 2017. Effort-Based Salary Support for PI Oversight Charges.
2. Cramer P. 2016. Investigator Compensation: Motivation vs. Regulatory Compliance. *Journal of Clinical Research Best Practices* 12(9). https://www.magiworld.org/Journal//2016/1609_Compensation_Rules.pdf
3. Gibson M. 2016. Developing an Investigator Compensation Plan. *Journal of Clinical Research Best Practices* 12(9). https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&cad=rja&uact=8&ved=2ahUKEwj81pmcsL70AhUloHIEHdeGCLQQFnoECAQQAQ&url=https%3A%2F%2Ffirstclinical.com%2Fjournal%2F2016%2F1609_Investigator_Compensation.pdf&usg=AOvVaw30RL0JLVKLcfsMUQNXLHfc
4. Goldfarb NM. 2010. Investigator Compensation by the Research Site.
5. AMA Code of Medical Ethics' Opinions on Clinical Research. 2015. *AMA Journal of Ethics* 17(12):1136–41. https://doi.org/10.1001/journalofethics.2015.17.12.coet1-1512
6. Fair Market Value Conundrum: Solutions for Sponsors and Sites. *Applied Clinical Trials*. http://www.appliedclinicaltrialsonline.com/fair-market-value-conundrum-solutions-sponsors-and-sites
7. Electronic *Code of Federal Regulations*. https://www.ecfr.gov/
8. In *Public Health. Title 42*. 2011. Office of the Federal Register, National Archives and Records Administration. https://www.govinfo.gov/app/details/CFR-2011-title42-vol2/CFR-2011-title42-vol2-sec411-351
9. *68 FR 23731—OIG Compliance Program Guidance for Pharmaceutical Manufacturers.* 2003. Office of the Federal Register, National Archives and Records Administration. https://www.govinfo.gov/app/details/FR-2003-05-05/https%3A%2F%2Fwww.govinfo.gov%2Fapp%2Fdetails%2FFR-2003-05-05%2F03-10949
10. Goldfarb NM. 2019. Why Fair Market Value is Not One Number. See also https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwi44InAsb70AhUfrHIEHVrIAIMQFnoECCAQAQ&url=https%3A%2F%2Fwww.magiworld.org%2Fjournal%2F2017%2F1712_FMV.pdf&usg=AOvVaw3TY-LmpHkjGmD8W67WQ-OM
11. Clinical Investigator Payment Best Practices. *Clinical Leader*. https://www.clinicalleader.com/doc/clinical-investigator-payment-best-practices-0001

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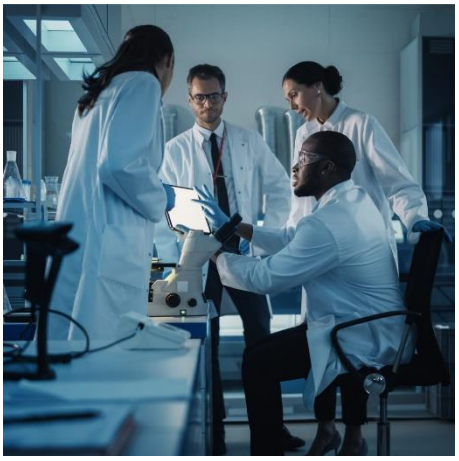
PEER REVIEWED

Points to Consider When Designing COVID-19 Treatment Study Protocols—Lessons Learned

Mostafa Salah, MSc, CCRP, ACRP-CP; Ola Elrouby, MSc; Mohamed Ayman, BPharm; Rehab Ahmed, BPharm



The urgent need for safe and effective treatment for COVID-19 infection and its related complications has driven the design of clinical trials aimed at finding a solution for this critical pandemic through screenings of already approved drugs and investigations of new candidates. The proper study protocol design could affect the validity of the results and the conclusions extracted from the study.

Background

According to the International Council for Harmonization's guidelines for Good Clinical Practice, any clinical trial should be conducted by following a previously approved protocol. This protocol demonstrates the detailed procedures for conducting the trial to achieve overall quality and ensuring validity of the study's conclusions.{1}

As the COVID-19 crisis lingers into yet another year, there is an urgent need for conducting well-designed and well-powered clinical trials for scientific evaluation of potential COVID-19 therapies.{2} In addition to the authors' own experiences in managing and conducting many COVID-19 trials, we have revised many published COVID-19 studies and regulatory authorities' guidelines regarding the development of products for treatment of the disease. What follows are several lessons learned from these experiences which we hope will help other researchers in designing their own proper clinical trial protocols for COVID-19 treatments.

Critical Points to be Considered Before and During Clinical Trial Protocol Development

Scientific rationale: The emerging pandemic allowed some sponsors and regulatory authorities to waive some applications for treatments from the normal development and approval pathway. Although this may shorten the pathway required for approval, some steps should not be waived. As an example, many pandemic-related clinical trials were initiated before conduction of proper preclinical studies to determine the most appropriate dose required in human subjects.

Further, many clinical trials were initiated based on docking or *in-vitro* studies or observations from some practitioners. This shortened pathway resulted in the investigation of many drugs without proper previously accepted pharmacokinetic/pharmacodynamic (PKPD) profiles. In one case, it was found that the required plasma concentration to achieve therapeutic effects could not be reached with a safe human dose.{3} This goes to show that clinical studies should be preceded by dose-response studies in animal or human models.

Endpoints: COVID-19 clinical trial protocols should feature endpoints which target the overall clinical status of patients, mortality rates, or need for intensive care unit admissions rather than targeting polymerase chain reaction (PCR) quantitative changes.{4}

PCR negativity is not a proper endpoint, especially in Phase III trials, as there is poor relation between the clinical outcome and the results of patients' PCR results. It was reported that many patients might still display SARS-CoV-2-positive PCR results up to weeks or months after clearance of the disease.{5} However, a quantitative PCR endpoint which depends on viral RNA level assessment might be useful in a Phase II clinical trial as a proof of concept for the efficacy of the investigational drugs. Another possible way is to perform viral conductivity assays to characterize the impact of treatment on shedding of cell culture infectious virus.

The most suitable way to detect the clinical effect of the investigational products, as we mentioned previously, should depend on the clinical picture of the patients and the disease progression status. The ideal endpoint to capture disease progression or improvement is the ordinal scale developed by the World Health Organization (WHO), which has already been used in many clinical studies, such as the SOLIDARITY trial.{6}

Monitoring of symptoms is important in COVID-19 trials but is better considered as part of secondary endpoints (especially in non-mild patients), as the administered COVID-19 treatment standard of care, which already contains several agents, may mask such symptoms of the disease as fever, cough, and arthralgia and bias the results of the study.

In mild out-patients, it may be acceptable to rely only on symptoms as an endpoint with the application of scoring for symptom severity at baseline and through the study process, as long as one considers how clinical findings show that certain symptoms (e.g., cough, fatigue, decreased sense of taste and sense of smell) may take longer to resolve in comparison to other symptoms.{7}

Further, change in lung lesions cannot be considered a suitable endpoint, as the published literature reveals that change may persist for a long time after the absence of all clinical symptoms and improvement in the patient's overall status has been achieved. In addition, lungs may take longer time for complete healing,{8} and it may be unethical to examine the patient several times by CT, as this may impact participant safety.

Meanwhile, when targeting detection of changes in oxygen saturation, the study design should take into consideration measurements of the saturation after removal of the patient's mask (room air recording). Recording oxygen saturation values when patients are masked may give higher values without the availability of a predictive tool to identify or estimate the true oxygen saturation percentage of the patient.

Finally, lab biomarkers such as IL-6, D-dimer, lymphocytes, or ferritin could be considered a sensitive endpoint to detect the severity of the disease in critical and severe infections, but these biomarkers may be of no value in studies for mild to moderate cases, as many reports stated that those patients might lack biomarker abnormalities through the disease course.{9}

Monitoring: The protocol and/or monitoring plan should consider the difficulty of performing onsite monitoring during the conduction of the study. A risk-based monitoring approach should be implemented to ensure verification of data and proper monitoring of the study conduction. The protocol should also specify the key critical data being sought in order to facilitate the monitoring process and achieve balance between accuracy and validity. This approach depends

on the availability of certain electronic resources to enable centralized or remote monitoring.{10}

Population: The protocol should clearly detail the eligibility criteria with consideration of the following points:

- Application of proper classification rules for disease severity, which can be extracted from either U.S. Food and Drug Administration guidelines{4} or WHO guidelines.{11} The inadequate categorization of patients may affect the validity of results or prevent the proper detection of the treatment effects due to the variability in subgroups' baseline difference, disease progression, or co-morbidities.
- The inclusion criteria should be extended to include patients with co-morbidities and advanced age, as these patients are more susceptible to disease progression with higher mortality rates.
- Studies of false-negative PCR results from respiratory samples for SARS-CoV-2 demonstrated that false-negative rates up to 30% may occur, which could be due to reasons including suboptimal specimen collection, testing too early in the disease process, low analytic sensitivity, inappropriate specimen type, low viral load, or variability in viral shedding. To overcome the impact of these false-negative results on the rate of enrollment, regulatory authorities in cooperation with researchers should apply other eligibility parameters to confirm COVID-19 infection, such as clinical symptoms or radiological chest scans. A useful criteria for clinical diagnosis of COVID-19 was recently published with suitable specificity and sensitivity in comparison to the PCR technique.{12}
- In general, the allowed time limit for onset of symptoms in enrolled patients should be prespecified in the protocol. Depending on the type of investigational products and their mechanisms of action, the allowed time limit for eligibility could be defined. Example: for antiviral drugs, it is better to enroll patients early, with up to 10 days from symptoms onset to capture the effect of the drug during the viremia phase.{13}

Concomitant medication: The protocol should closely address the PK/PD interactions between any of the investigational products and any agent from the standard of care protocol, as many drugs have been found to affect the efficacy of investigational products after further study.{14}

Conclusion

Proper protocol development is critical to ensure the validity and reproducibility of clinical trial results, especially in pandemic emergencies such as we've seen from COVID-19 infection. Large and accurate literature reviews should be performed to collect all available data to strengthen the design of protocols. Sponsors and researchers should consider the points raised above during the protocol development phase.

References

1. ICH GCP E6(R2) guidelines: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
2. Rai SN, Qian C, Pan J, Seth A, Srivastava DK, Bhatnagar A. 2020. Statistical design of Phase II/III clinical trials for testing therapeutic interventions in COVID-19 patients. *BMC Medical Research Methodology* 20:Article 220.
3. Bray M, Rayner C, Noël F, Jans D, Wagstaff K. 2020. Ivermectin and COVID-19: A report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Res* 178:104805. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172803/
4. FDA guidelines: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry. 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention
5. Public Health Agency of Canada guidance for repeated PCR testing in individuals previously positive for COVID-19. 2020. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/repeated-pcr-testing-individuals-previously-positive-covid-19.html
6. WHO interim analysis results. 2021. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. *N Engl J Med* 384:497–511. https://www.nejm.org/doi/full/10.1056/NEJMoa2023184
7. FDA guidance: Assessing COVID-19-Related Symptoms in Outpatient Adult and Adolescent Subjects in Clinical Trials of Drugs and Biological Products for COVID-19 Prevention or Treatment Guidance for Industry. 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs
8. Hefeda MM. 2020. CT chest findings in patients infected with COVID-19: review of literature. *Egyptian Journal of Radiology and Nuclear Medicine* 51:Article 239.

9. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, Gabrilove JL, Sacks H. 2021. Biomarkers and outcomes of COVID-19 hospitalizations: systematic review and metanalysis. *BMJ Evidence-Based Medicine* 26(3). https://ebm.bmj.com/content/26/3/107
10. FDA guidance: A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry. 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/risk-based-approach-monitoring-clinical-investigations-questions-and-answers
11. WHO guidance: COVID-19 clinical management. 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1
12. Cadegiani FA, Zimerman RA, de Souza BC, McCoy J, E Costa RAP, Wambier CG, Goren A. 2021. The AndroCoV Clinical Scoring for COVID-19 Diagnosis: A Prompt, Feasible, Costless, and Highly Sensitive Diagnostic Tool for COVID-19 Based on a 1757-Patient Cohort. *Cureus* 13(1):e12565.
13. Tana C, Biao S, Jian LY, Meizhu L, Liu CJ. 2020. SARS-CoV-2 viremia may predict rapid deterioration of COVID-19 patients. *The Brazilian Journal of Infectious Diseases* 24(6):565–9.
14. New potential interaction with emergency COVID-19 medicine remdesivir. 2020. Nature public health emergency collection. *Reactions Weekly* 1810(1):3. doi:10.1007/s40278-020-80023-6

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Clinical Researcher—December 2021 (Volume 35, Issue 9)

SPECIAL FEATURE

How and Why Bayesian Statistics Are Revolutionizing Pharmaceutical Decision Making

Bruno Boulanger, PhD; Bradley P. Carlin, PhD

Over the past 20 years, there has been growing interest within the pharmaceutical industry in Bayesian statistics and how to apply this methodology toward reaching goals in the arenas of research, development, manufacturing, and health economics.

The Bayesian approach to pharmaceutical decision making started to gather greater momentum after the first Applied Bayesian Biostatistics conference in 2010, which brought together academicians, industry representatives, and regulatory authorities to discuss the practical implementation of Bayesian statistics in speeding up drug discovery, development, and approvals. Increasingly, pharmaceutical companies have been turning to Bayesian biostatisticians to apply probabilities to statistical problems to determine likely outcomes—in clinical trials, in product development, in manufacturing, in post-market surveillance, and in market access.

While regulatory authorities have been slower to adopt Bayesian methodologies, that is starting to change. The U.S. Food and Drug Administration (FDA), in particular, has embraced Bayesian statistics as a method for supporting clinical trials in medical devices, in adaptive clinical designs, and in rare diseases.

This paper explores the growing significance of Bayesian statistics in supporting decision making across the development and regulatory processes, and its potential to improve outcomes for the biopharmaceutical industry.

How an 18th Century Methodology is Gaining Traction Today

For more than a half a century, traditional frequentist statistical methodology—where predictions are based on a fixed target of estimation—has been entrenched in clinical development and regulatory statistics. Yet, all too often drugs fail late, even in confirmatory clinical trials, at enormous cost to companies and ethical concerns for the patients, suggesting some shortcomings in these traditional methods.{1} As pressure to reduce costs and improve regulatory decision making early in the process intensifies, companies have sought more efficient ways to analyze data and assess the safety and efficacy of drugs.

It turns out that one of the most effective tools for synthesizing clinical trial data is far older than even the clinical trial process itself: Bayesian statistics.

Bayes Theorem was formulated by the Rev. Thomas Bayes, an 18th century English mathematician, philosopher, and Nonconformist minister. However, it wasn't until the 1990s, when advances in computing technology emerged, that its techniques could be usefully applied.

Interest within the pharmaceutical industry in applying Bayesian methods at various stages of research, development, manufacturing, and health economics has been growing for the past 20 years because it applies the logic of probability to statistical problems, based on observed data.{2}

Comparing Statistical Methods

Mathematical methods have long been used to assist with decision making in clinical research, with researchers often depending on the *p*-value, or observed significance level, to test whether something is statistically significant. The point is to determine the significance of the results from a study in relation to the null hypothesis, which states there is no difference between two variables. If the data sample size is big enough, then the distribution of the test statistic is roughly normal (bell-shaped) and can give you the *p*-value. However, if there isn't a large sample of data, it becomes impossible to produce a reliable inference.

For example, if researchers are gathering disease rates by county or state, it's relatively easy to gather good estimates in urban areas, but in sparsely populated rural areas, the estimates are not necessarily reliable. Two breast cancer cases in one small area in a year may raise suggestions of a cluster because, based on traditional statistical methods, the resulting rate is far higher than expected; seeing zero cases a year later would be just as uninformative. To make sense of the data, statisticians have to smooth the spatial maps and produce a more accurate picture of those cancer rates.

Bayesian methods help to achieve this by borrowing strength from observations across similar but not identical bits of information; for example, cancer rates across the map in question. In Bayesian statistics, previous and related information is relevant. Past information—whether from previous trials, scientific literature, or real-world data—is considered as part of an ongoing stream of data, "in which inferences are being updated each time new data become available."{3} This allows researchers to achieve direct probability statements about unknown information, rather than settling for approximations.

Why Bayesian Makes Sense in the Pharmaceutical World

What, though, does all this mean for clinical trials and drug development? As everyone in the industry knows all too well, the drug approval process is costly, complex, and time-consuming. During clinical trials, companies need to know whether a drug under development is safe and effective, as well as its likelihood of success in the marketplace. This is where Bayesian methodology comes to the fore. It addresses the probability inference: What's the probability that this new drug is safe and effective? What is the probability our current drug development program will be successful?

In most development programs, companies already have some information about a molecule or therapy from previous studies, either conducted by that company or by others. Rather than start from scratch, Bayesian statistics allow researchers to leverage this pre-existing information—including from scientific literature—to help determine the probability of success.

When a trial is conducted using Bayesian principles, initial estimates of probabilities are attributed to unknown quantities (the likelihood of a serious event, the likelihood the product will be effective for a

given set of patients, etc.) using existing information (e.g., previous clinical trials) or expert opinion. These probabilities together constitute the *prior distribution* for the quantities of interest.{3}

As long as those conducting the study construct the prior distribution in an unbiased way (i.e., incorporating all existing knowledge, not merely that which is favorable to the company's position), leveraging this information to support a study can dramatically improve study accuracy and efficiency. It is also economically and ethically preferable to limit the number of in-human studies conducted whenever possible.

Regulators can sometimes be somewhat more rigorous when it comes to Bayesian analyses, because they are less familiar with it than the traditional *p*-value approach. However, this tends to encourage careful, less automatic analyses that are typically very robust, and more formally consider the impact of multiple different models and assumptions.

That is not to suggest that Bayesian methodologies are a replacement for *p*-values, which answer a fundamentally different question than Bayesian probabilities. "The *p*-value quantifies the discrepancy between the data and a null hypothesis of interest, usually the assumption of no difference or no effect. A Bayesian approach allows the calibration of *p*-values by transforming them to direct measures of the evidence against the null hypothesis, so-called Bayes factors."{4}

For example, in a genomics experiment, researchers will put some of the drug or molecule into cells to assess the expression of different genes. The question in this case will be, is the inhibition or excitation of the genes likely linked to the treatment? Here, researchers may legitimately be interested in the *p*-value; they want to know if the data they see are inconsistent with the hypothesis of no differential inhibition or excitation across genes. In such cases, *p*-values provide fairly straightforward yes-no answers because the very question is about the observed data.

However, *p*-values have a number of problems that limit their effectiveness even when used correctly. This was emphasized a few years ago by the American Statistical Association (ASA), which released an official "Statement on Statistical Significance and *P*-Values,"{5} and later held two conferences devoted to an investigation of their problems and potential remedies—many of them Bayesian. The ASA statement emphasizes various misconceptions about *p*-values, including the facts that they are not the probability that the null hypothesis is true, or the probability that the data were obtained "by chance

alone" (two very common though falsely held beliefs). *P*-values do not measure the size or importance of an observed effect and can only provide evidence against a hypothesis of no difference, not evidence for it. As such, *p*-values are not useful in proving the equivalence of two treatments.

When conducting a clinical trial or animal study to evaluate the efficacy of a treatment, the question is not about the data itself, but rather about the treatment: Is the treatment effective? Is it safe? How likely is it that a trend emerging in the data will continue in the future? This is where Bayesian methodology has even greater usefulness. To predict a future situation, Bayesian statistics enable researchers to determine the probability of something occurring by first quantifying current uncertainty, and then propagating that into the future to get predictive probabilities. The question then is about the benefit for future patients in future trials or in the real world (i.e., not for the patients included in the past trials).

This current and future uncertainty is common in chemistry, manufacturing, and controls (CMC) applications where companies need to be able to quantify what they know now about product characteristics or manufacturing processes and combine that with additional uncertainty about what will happen in the future. It allows researchers to address the real questions of interest: Is a process comparable to a previous one? What is the probability that a development approach is on target given the observed data?

Bayesian statistics combine all that complicated and high-dimensional data, and, using 21st century computing power and experts in mathematical probability theory, develop modeling to predict a likely future outcome.

Supporting Decision Making in a Competitive Market

The enormous cost of bringing drug products to market, combined with the shift away from blockbuster product development and toward personalized medicines, often targeting rare diseases, means the paradigm for product development is changing. The past practice of using trial and error to make decisions about clinical trials, manufacturing processes, regulatory practices, or any other part of the pharmaceutical value chain is proving to be highly ineffective.

Regulatory leaders also recognize the need for new methodologies to support clinical trial design. For example, the FDA has issued guidance for industry on Complex Innovative Trial Designs (CIDs) for

Drugs and Biological Products, providing advice on interacting with the agency in the development and regulatory review of such products.{6} As the guidance notes: "Bayesian approaches may be well-suited for some CIDs intended to provide substantial evidence of effectiveness because they can provide flexibility in the design and analysis of a trial, particularly when complex adaptations and predictive models are used. In addition, Bayesian inference may be appropriate in settings where it is advantageous to systematically combine multiple sources of evidence, such as extrapolation of adult data to pediatric populations, or to borrow control data from Phase II trials to augment a Phase III trial."

Sometimes a drug might work for one patient population but fail with another, and there may be multiple reasons for that, including some tied to patients' behaviors. As an example, at the outset of the AIDS epidemic in the 1980s, the majority of clinical trials were conducted on predominantly gay men from San Francisco and other diverse, urban areas. These men were largely compliant in their trial behavior: they stayed on their assigned treatments and dramatically reduced their risky behaviors. The result was these early trials were able to show that the drugs worked. Later in the epidemic, however, when different populations started getting HIV (for example, IV drug users from economically disadvantaged neighborhoods), these groups were sometimes less able to comply with rigid trial protocols. The result was that drugs already approved by regulators for treatment of HIV did not work in the "real worlds" of these later patients. An effective statistical approach must adjust for these differences.

What Bayesian inference allows researchers to do is, rather than keep conducting randomized trials, adjust for individual characteristics—based on where a patient lives, how old they are, their gender, their doctor, their socioeconomic status, drug use, etc. By adjusting for those real-world, confounding variables, Bayesian enables an innovative approach to data analysis with a focus on solutions.

Most important is that by leveraging prior knowledge—from previous clinical trials, scientific literature, or real-world data—Bayesian statistics allow researchers to reduce the number and size of clinical trials and help to determine the probability of success before entering Phase III trials. It does this by injecting flexibility into the way the trial is designed, to ensure projections aren't overly optimistic, thereby accounting for the probabilities of unknown issues occurring.

Changing the paradigm of clinical trials is not only more practical and financially beneficial, but also potentially more ethical, particularly when conducting studies into treatments for rare or pediatric diseases. Not only are researchers working with a much smaller sample size of patients, but they are also working with very vulnerable patients. In some diseases, for example, life expectancy of the patient may be very short, and including a randomized parallel control study arm would strike many as unethical. Instead, by leveraging information from past studies and the literature, researchers can eliminate or at least dramatically reduce the need for a control group and ensure new treatments are tested on the patients who really need it. Bayesian statistics support that cumulative learning process by connecting the dots across different studies to support decision making in a formal way.

Bayesian methodology can also help companies make economic decisions, such as whether to build a manufacturing line for a drug in development. This is a difficult decision: If the company decides to invest in building its facility early and a drug fails in clinical trials, that investment is wasted. On the other hand, building a plant can take several years, and if the company waits for regulatory approval to begin building the facility, it will be years before that company is able to sell the approved product. Using Bayesian statistics, it is possible to compute the future probability of success during the Phase III trial and make a risk-based economic decision from that assessment.

Similarly, in portfolio management, Bayesian methodology can help companies to compute the probability of success of each of their compounds and thus decide where to invest future resources. The point is that the methodology can assist companies with making smart investment decisions through its ability to estimate probabilities of future success.

Into the Future with Bayes

The pressing needs of both companies and patients to improve the framework for making decisions has led many biopharmaceutical companies to seek out statistical experts specializing in Bayesian methodology. Many recognize the potential Bayesian statistics present to address complex problems that arise across the product lifecycle—from the probability of success with clinical trials to managing CMC and supply chains to determine the best course of action with the product portfolio.

More recently, the Bayesian momentum has gathered pace. In 2010, the first Applied Bayesian Biostatistics conference was held with a goal of stimulating the practical implementation of Bayesian

statistics for the purpose of accelerating the discovery and delivery of new cures to patients.{2} That conference and others brought together a wealth of insights and knowledge that formed the basis for an award-winning book offering an overview of Bayesian methods applied to nearly all stages of drug research and development. The book, entitled *Bayesian Methods in Pharmaceutical Research*, was announced as the 2021 winner of Best New Bayesian Statistics Book, Best New Biostatistics Books, and one of the Best Statistics eBooks of all time by BookAuthority.

Insights from the book and from experts in the field of Bayesian statistics and their applications in the pharmaceutical industry will play an important role in improving understanding of ways to apply statistical methods to pharmaceutical problem solving.

References

1. Ruberg SJ, et al. 2019. Inference and Decision Making for 21st-Century Drug Development and Approval. *The American Statistician* 73:319–27. https://www.tandfonline.com/doi/full/10.1080/00031305.2019.1566091
2. Lesaffre E, Baio G, Boulanger B. 2020. Bayesian Methods in Pharmaceutical Research, CRC Press/Taylor and Francis Group.
3. U.S. Food and Drug Administration. 2010. Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials.
4. Held L, Ott M. 2017. On p-Values and Bayes Factors. *Annual Review of Statistics and its Application* 5:393–419. https://www.annualreviews.org/doi/10.1146/annurev-statistics-031017-100307
5. American Statistical Association releases statement on statistical significance and *p*-values. 2016. *ASA News*. https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf
6. U.S. Food and Drug Administration. 2020. Interacting with the FDA on Complex Innovative Clinical Trial Designs for Drugs and Biological Products, Guidance for Industry.

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Clinical Researcher—December 2021 (Volume 35, Issue 9)

OPINION

Raising Awareness of Clinical Trials in Diverse Communities

LaQuinta Jernigan

I am from a diverse community, and it is important to me that my family is well represented in clinical research so we can have the best treatments and therapies available to us.

My sister has a rare disease and growing up we went through years of treatments trying to find answers. It is only now, finding myself working in the clinical research enterprise, I realize life could have been a lot easier if we had decided to participate in a clinical trial. However, at the time, we lacked the awareness or the access necessary to pursue that option.

If we can solve this challenge, we can change the trajectory of peoples' lives for the better.

I recently discussed how we can raise awareness of clinical trials in diverse communities with Dr. Allison Matthews, CEO and founder of Community Expert Solutions, and Rashaad Galloway and Dezbee McDaniel, cofounders of CliniSpan Health. We considered the scale of the challenge, three key barriers to diversity (awareness, accessibility, and trust), and what the industry can do to help.

The Challenge

Diversity in clinical research is both a scientific and ethical issue. Of key importance from a scientific standpoint is the fact that study data are incomplete if diverse communities are left out.

At the moment, drugs are still being approved and reaching the market with little data for minority communities. In a review of 230 oncology clinical trials taking place between 2008 and 2018, only 145 included any information about the participant's race. Of those that did, approximately 76% of the participants were white, 18% Black, 3% Asian, and 6% Hispanic. Without data from all of these groups, we cannot be certain a treatment works for everyone.

A 2014 study in *Clinical Pharmacology & Therapeutics* found variations in how people from different ethnic groups reacted to around 20% of new drugs approved between 2008 and 2013. Dr. Matthews says people of color react differently to drugs not because of inherent biological difference, but because of lived experience; for example, people of color tend to have higher rates of stress and higher exposure to environmental toxins—a key reason why they must be engaged in clinical research.

Ethically, it is our duty as an industry to work to remove disparities in healthcare, making it accessible for all. We must make sure nobody is left out.

Awareness

Certain communities are extremely close-knit; their members tend to stay within the same areas, go to the same physicians, and get their information from the same places—perhaps a church or community center.

Clinical research in many areas may be confined to large teaching institutions, meaning sites like local hospitals or community centers servicing these minority populations are not asked to participate in clinical trials. Further, most patients are referred to clinical trials by a physician. If we are not reaching local hospitals, how can we hope to reach their patients?

We must build awareness on a community level to increase participation from both patients and healthy volunteers. A new obstacle on the path to such awareness is that COVID-19 has allowed everyone to recognize what a clinical trial is, but has also led to misunderstandings about the medical research process.

“A lot of people are equating medical research with” COVID-19 vaccines right now, said Dezbee. “That’s the most recent thing that has given people a reason to have mistrust, and it’s what a lot of patient conversations are centered around.”

Extensive public education has been necessary to get people to take the vaccines and explain what a clinical trial journey looks like. However, education cannot stop just because we have vaccines. If there had been more clinical trial awareness to start with, we wouldn’t have had to go to these extremes.

We need public health initiatives telling people how they can participate, how they can contribute, and how clinical trials benefit not only them but the greater good.

Accessibility

Even if a patient from a diverse community is referred to a trial, they will likely have to travel long distances to participate. They may have to take time off work and may not have access to the resources necessary to enroll in a study for which they are qualified.

“Research institutions are not set up in a way that makes it convenient and efficient for people of color to participate in research,” said Alison. “We need to really take a hard look at how we can do better to accommodate and make [participation] more accessible for people in the community.”

To make clinical trials truly accessible to the broadest range of people, we need to start thinking about protocol design from the everyday person’s perspective. We need to ask, is this going to be feasible? Can they participate in these visits on this frequency? If they read the protocol, will they understand what is required of them?

Addressing these considerations within protocols is the only way to make trials more accessible to these groups.

Trust

When it comes to clinical research, there are a lot of trust issues from the past, including histories of abuse within some communities. We have been naive to think these trust issues are over.

“Trust and accessibility are equally important, but trust has to come first,” said Dezbee. “It’s the rapport you build with a potential patient that leaves them open to being educated about clinical trials, and open to exploring access. Once you have built that with them, you then become partners in trying to create accessibility.”

We must make sure everyone, no matter their gender or race, receives the same treatment and standard of care everywhere. If we do not address these issues, there will not be enough trust for people to participate in clinical trials where they don’t know what the outcome is going to be.

The only way we are going to tackle trust is to make sure we are having genuine conversations with community leaders and their organizations.

Dr. Matthews said: “Make sure that you have a continued presence in the community. Don’t just come in and ask for what you need, and then leave. Be a resource for them and support their initiatives as oftentimes, they’re doing work in the community that goes unfunded and unsupported.”

Industry-Wide Action

This is not a problem that is going to be solved individually. We need to work together to figure out the best way forward. In this industry, we want to find solutions that are tried, tested, and true—but we must try new things because this is a problem we have not solved yet.

“One of the first things that needs to happen is the inclusion of people of color in the research process—not only as participants but as administrators and facilitators,” said Rashaad. “We need more black doctors because black people trust black doctors—people of color trust the people who look like them.”

Big pharma also needs to engage the small, grassroots organizations that are organically tackling this issue. Most of these organizations are small and localized, but they are powerful. They have the ear of the community, and they have innovative ways to reach its members.

Further, we need to make sure all clinical trials are collecting data on ethnicity. Without the data, we cannot see progress.

Finally, we must make clinical trials accessible to all sites, of all sizes.

When recruiting sites, large academic institutions are still important, but we also need to find smaller, under-the-radar sites. That might take more work, it might take an education effort, and it might take training—most of these sites have probably never participated in a clinical trial, but it will be worth it.

One Foot in Front of the Other

If we consider everything that needs to be done on a legislative and regulatory level, it can feel overwhelming. However, if we take little steps, those little steps will add together, they will result in small outcomes, and those small outcomes will result in bigger changes happening.

We cannot allow ourselves to be overwhelmed by everything that needs to be done. We need to start wherever we can. The fact we are having these discussions on an industry level is progress in the right direction.

Hopefully, five years from now, we can look back and say, "Wow, look how far we've come."

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Clinical Researcher—December 2021 (Volume 35, Issue 9)

SITES & SPONSORS

A Chance Encounter: When CRAs and Study Patients Meet

Elizabeth Weeks-Rowe, LVN, CCRA

When I transitioned from being a study coordinator to the clinical research associate (CRA) role, I understood that I would no longer interact with study patients. The shift to industry signified the end of the face-to-face patient engagement that I would deeply miss. For me, one of the highlights of being a coordinator was developing relationships with study patients through the educational aspects of informed consent, and through learning a patient's history during intake and their overall story during subsequent study visits.

Patients entrust study coordinators with their health, and coordinators rely upon their transparency to ensure patient safety and credible data collection. This reciprocity creates a partnership framed by compassion, understanding, and the aligned goals of health/discovery unique to the study patient/practitioner relationship.

The View from the Other Side

I was grateful for the next step in my clinical research career and accepted that I would now become acquainted with study patients via source/medical record review during monitoring visits. I became an oncology monitor early in my CRA career, which required me to learn difficult drug calculations, Response Evaluation in Solid Tumors (RECIST) criteria, and the fine points of identifying inconsistencies in pathology/lab results. This created a solid foundation for understanding diverse disease processes.

The first oncology study to which I was assigned was a Phase III advanced solid tumor study with a randomized, double-blind design. The patients were all treated with standard of care chemotherapy and then either assigned to investigational drug or matching placebo. The investigational agent targeted tumor growth, and there had been incredible results in the previous trials conducted. This was the pivotal trial, with extensive patient assessments to support the critical endpoints. It was my responsibility as the CRA to ensure the procedures had been completed in compliance with the protocol, and this was a task I took very seriously.

The investigational sites to which I was assigned varied from large academic health institutions with high enrollment numbers to smaller oncology medical practices with understandably fewer patients. One of my favorite sites was a small oncology practice with two physician oncologists who took turns serving as principal investigator (PI) on the studies they conducted. They did not conduct a large number of studies; the primary study coordinator was their only full-time employee, and she was backed by a part-time research nurse and the medical office manager/research administrator.

The research department was part of the medical practice and study patients were seen in the same clinic area as the practice patients. The research department was located beyond the patient examination areas and consisted of a large room that housed the coordinator's work area, the lab processing area, and study drug storage and supplies. The monitoring space was the investigator's office, or an empty desk in the back of the research department. Study assessments such as imaging and local safety labs were completed at the hospital next door to the practice.

Though the research space was small, they leveraged their resources to conduct ethical, quality research. They had only enrolled three patients in the study, all of whom were still in the treatment phase. The atmosphere at this site was warm, without formality, and the study patients were treated like family. They would frequently walk back to the research work area to greet the study coordinator and other staff before their study visits began. Their participation in the study, even if it did not benefit them, would help further research/treatment for their disease.

Though I did not know these patients, I knew their stories of courage and sacrifice from review of their medical records, and by allowing this review, these patients had helped me become proficient in tasks that were crucial to my role. After a difficult day, reading their charts gave me time for perspective, pause, and a reminder of what was truly important in life.

Live and in Person

"Larry" was a study patient whose story touched me deeply. He was in his late 60s and had been on the study for about a year. Though no one knew, in theory, to which treatment he had been assigned, he was steadily improving. His lab values were within normal limits and his tumors were shrinking. His status was steadily changing from terminal to recovery, and the narrative of each study visit described his joy. His gratitude came alive from the dictated notes in the medical record I reviewed. I never imagined I would witness it in person.

During a routine monitoring visit, I was reviewing data queries with the study coordinator at her desk when a gentleman sporting a Yankees tee shirt and a happy demeanor entered the room. The coordinator introduced me as the monitor for the study in which he was participating. Before she could utter his name, I knew this was Larry, and I was a little dumbfounded that I was being introduced to a study patient, not to mention that this was Larry in the proverbial flesh.

He smiled, shook my hand, and without hesitation informed me that he knew he was on the study drug. Next followed a straightforward testament of his improving health and outlook due to study participation. "Your company is doing a remarkable thing," he said. "I have never felt better and am taking my grandson to a baseball game next week." I struggled to reply, but managed to thank him for his words and study participation before the coordinator escorted him to the examination room for his study visit. I stood rooted to the spot, alternatively stunned and grateful over this rare encounter.

What once lived only in the pages of a medical record—Larry's story with its reams of paper representing diagnosis, devastation, treatment, illness, set back, and recovery—had come alive to me with that introduction, and his testament regarding the miracle of clinical research. I had the honor of witnessing the most pivotal chronology of his life, revealed willingly in the name of discovery. That moment represented one of the main reasons why I work in clinical research; the path of discovery that results in hope and healing to patients in need.

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Clinical Researcher—December 2021 (Volume 35, Issue 9)

RECRUITMENT & RETENTION

Top 5 Tips for Collaborating with Patient Advocacy Groups for Your Patient Recruitment Efforts

Contributed by Leapcure

In times like these, when there is both a great fear of the unknown and a great push for innovation, patients need to have trust in their medical institutions and healthcare providers. Without the proper trust when so much is at stake, study sites will not be able to get willing patients in the door to participate in vital clinical trials and other studies of innovations in medicine and different therapeutic methods.

There needs to be transparency and proper communication between the patient, doctor, and researcher. This is why patient advocacy groups are so essential to patient recruitment. These groups provide a platform in which patients are the experts on their condition, and by working with a patient advocacy group, they can be connected with sites running potentially beneficial clinical trials.

Still, for certain rare conditions, there just might not be many patients available, and perhaps even fewer who are willing to enter into clinical trials and experimental treatment. Rare illness and disease can be an alienating experience, with many ups and downs. By working with advocacy groups, study sites can be assured that they are working with patients who are accounted for, cared for, and eager to participate in innovative, cutting-edge clinical trials as well as to provide insights into the research process. Here are some tips for site leaders who wish to collaborate with a patient advocacy group.

Be Patient-Minded

The patient should be the central focus of any healthcare and research practice. Especially now, as patients have become used to communicating with each other; there are online forums, discords, and subreddits in which people with particular conditions will share their experiences with and opinions on the latest innovations and clinical trials to treat their conditions.

Put simply, you want to ensure that your patients are as happy—within reason—as they can be. Of course, medical treatment might not always be pleasant, but taking a compassionate approach and showing the patient that he or she is the most important person in this process is essential in recruiting patients. It also helps build trust between sites and patients—a trait that is critical to this partnership.

Run an Audit of the Patient Advocacy Group

Whatever research you are conducting, you need to make sure that the patient advocacy group you are working with is the right fit for you and your team. For finding a patient advocacy group to work with, make sure you do some preliminary research—what is the group's mission, audience, vision, issues, programs, campaigns, and stakeholders?

You should run those audits on several different patient advocacy groups and then create an inventory of your findings. Now you have a catalog of different patient advocacy groups to select from. The next step might be conducting phone interviews with each group, in which you will probe further into the nature of their missions, details on who they work with, and clues as to whether they will be a suitable fit for you and your team.

Remember, patient advocacy groups are not a one-size-fits-all type of business. There is a spectrum of players out there, and you need to do your research to ensure that you are working with the right group. The better your background research, the better you will be able to determine whether a group's mission aligns with yours.

Find Mutual Points of Interest

When conducting business as sensitive as medical research, the cooperating parties need to have some alignment with each other, especially in terms of mutual points of interest. By having mutual points of interest, you can have confidence in the reciprocation of whatever deal has been agreed upon. You want to make sure that other stakeholders have a real interest in maintaining the relationship you have entered.

This point harkens back to the importance of running an audit: You want to make sure that you have some similar motivations so that you might have a similar goal in mind. If your goals and desires are totally out of line with each other, then conducting medical research together might not result in a fruitful relationship.

Elevate Transparency to a Best Practice

When working with doctors, patients, and other stakeholders, you want to make sure that you are being transparent and that this transparency is obvious to all stakeholders. Transparency means trust and honesty, and that is exactly what a patient and a patient advocacy group want to see in a medical team; they do not want to feel that some vital information is being left out of the conversation. To build strong relationships with patients and other stakeholders and a strong reputation in your respective medical community, it is essential to build a sense of trust and transparency.

Make a Commitment

If, after agreeing to work with a patient advocacy group, you suddenly pull out of the relationship, you can be sure that the group—and perhaps others—will be wary of working with you ever again. On the other hand, if you follow through on your commitments and are a trusted partner for the duration of the relationship, then that patient advocacy group—and perhaps others—will be excited to work with your team. After all, real progress in medicine can only happen if there is trust between the stakeholders; if there is not, nothing will get done, and patients or other stakeholders will withdraw from the deal.

Conclusion

By working with a patient advocacy group, you can gain a much better handle on managing relationships with patients and other stakeholders. However, you do not want to work with a patient advocacy group without ensuring that you have similar interests and goals in mind. It's not always an easy process to follow, but not only can you facilitate finding willing patients in concert with the right patient advocacy partners, the extra work involved might be essential for the sort of research you and your team plan to conduct.

Through an honest commitment, heightened levels of transparency, and a patient-centered approach, you can reap great benefits and open the door to many great relationships with patient advocacy groups and patients alike.

Contributed by Leapcure, an organization devoted to working with patient advocacy groups and clinical trial sites to connect patients to research opportunities around the world.

Clinical Researcher—December 2021 (Volume 35, Issue 9)

OVER THE TRANSOM

To Face Unafraid the Plans That We've Made…

Gary W. Cramer

As one year winds down and people begin to look forward to the challenges and adventures of the new year to come, it is not uncommon for big announcements to be part and parcel of building the anticipation. If this were a lifestyle or entertainment magazine, I'd regale you with snippets of press releases about the most exciting weddings or movies to save the dates for in 2022. However, we are dealing with the somewhat less glamorous world of clinical research in these pages, so for my parting gift to you this year you'll have to settle for these businesslike, but still-intriguing, alerts about several recent partnerships that have formed to further the development and conduct of trials for the benefit of humankind (no endorsements implied). May your new year be as bold!

Alliance Aims to Deliver on Promise of Fully Integrated Research Networks

U.S.-based IACT Health and Canada-based LMC Manna Research in November announced a strategic alliance to integrate their operations. As two of the clinical research industry's most extensive site networks, the alliance creates one of the largest consolidated research networks in North America, with more than 40 sites, access to more than 1.5 million patients, and more than 150 active investigators.

IACT Health, the largest network of wholly owned clinical research sites in the southeast U.S., since 2005 has contributed to helping more than 80 medications achieve U.S. Food and Drug Administration approvals in areas such as oncology, cardiology, pulmonology, endocrinology,

infectious disease, and pain. As Canada's most extensive clinical research network, LMC Manna Research provides pharmaceutical companies and contract research organizations with a single-source approach to performing clinical trials across a full gamut of treatment areas.

The combined IACT LMC Manna further announced in December that it had merged with True North Clinical Research, a two-site network focused on central nervous system studies and based in Halifax, Nova Scotia, Canada.

Partnership to Focus on Open Innovation Solutions to Advance Diversity in Trials

Two veteran-led businesses announced a critical partnership in November designed to use open innovation to advance diversity in clinical trials. Ibility, LLC and IndyGeneUS Health have partnered to amplify a shared mission of working with Historically Black Colleges and Universities, Minority Serving Institutions, and the Veteran community to advance health equity by diversifying clinical trials and maximizing the value of their genetic data for their benefit and for the global population.

The companies look to harness the power of challenge competitions to crowdsource solutions involving communities of people that have been systematically underrepresented in clinical research to address the challenges associated with diversifying clinical trials. Challenge competitions are used to ignite the creative process by building interdisciplinary teams around an end-user in a fun and engaging way.

Expanding Direct-to-Patient Testing and eCare for Decentralized Clinical Trials

Medable Inc. and Vault Health, Inc. in December announced that they are teaming up to integrate Vault's expertise in diagnostics, logistics, and remote care services with Medable's end-to-end software platform for decentralized clinical trials. The partnership combines a software-as-a-service platform with tech-enabled operational capabilities to provide a unified experience for patients, sites, and clinical trial sponsors in terms of home healthcare visits and televisits, virtual site capabilities, and related logistics, scheduling, and status tracking.

"The future of clinical research is decentralized—whether that's in a traditional clinic, a virtual site, a local pharmacy, or someone's home," said Dr. Michelle Longmire, CEO and co-founder of Medable. The partnership aims "to make clinical trial participation much more convenient for patients—providing them with easy testing and diagnostic options, as well as expert remote care they can access from anywhere," she adds.

CRO Merger Looks to Expand Global Reach and Capabilities

Rho, a full-service contract research organization (CRO) based in North Carolina, announced in December that it had acquired Dokumeds, a privately held European CRO. Established in 1995 and headquartered in Riga, Latvia, Dokumeds has 10 offices and is active across multiple continents. Terms were not disclosed.

Saying that the companies "are a great match," Laura Helms Reece, DrPH, CEO of Rho, added that the teams "are already aligned, ready to drive sponsors' multinational programs forward to achieve development milestones and bring new and better treatments to patients."

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