Clinical Researcher—November 2020 (Volume 34, Issue 9)

SPECIAL FEATURE

Career Advice from Research Veterans, Part 1: Focusing on the Fundamentals

Collected by James Michael Causey, Editor-in-Chief

To say the state of clinical research is in flux is something of an understatement. A global pandemic has changed our professional and personal lives in ways we couldn't have imagined at the beginning of 2020. At the same time, new technologies, evolving regulatory expectations, and pressures to handle increasingly complex trial protocols make the clinical researcher's job a challenge like no other.

However, the upside is clear: Answering to a higher calling by working to develop the medicines, devices, and treatments that ease suffering, prolong life, and provide a new hope where none may have existed before.

Clinical Researcher reached out to members of ACRP's Association Board of Trustees (ABoT) and the Academy of Clinical Research Professionals Board of Trustees, and to the ACRP Fellows to share the collective wisdom and insights that helped them propel their own careers forward. In the following responses, these thought leaders emphasize a number of key skills and approaches they found helpful at various stages of their journey.

However, a successful career might ultimately begin with attitude, suggests **Paul Evans, PhD, president and CEO at Velocity Research and the 2020 Chair of the ABoT.** "It doesn't matter what you do, just be passionate about whatever you do," Evans says. "You are far more likely to be successful and you will enjoy it more."

Anne Blanchard, CCRA, a clinical research executive consultant with LATINABA in Latin America and ABoT member, offers up a simple, yet powerful idea: "Always remember that research subjects could one day well be your family or yourself, and without volunteers and patient/volunteers, clinical research would not be possible."

Here are some of the other best ideas shared by the group:

Janet Ellen Holwell, CCRC, CCRA, TIACR, FACRP, a clinical research consultant/trainer: Say "YES!" Yes to every opportunity afforded you. The more experience gained, the more useful it will be in your future. There are many opportunities while working for a smaller company where one can wear many hats, but even in larger organizations there are opportunities if you seek them. Volunteer to cover for others or apply for a secondment if offered.

Michael R. Hamrell, PhD, RAC, FRAPS, CCRA, RQAP-GCP, FACRP, president of MORIAH Consultants: Stay current with technology, both hardware and software. There will continue to be new developments in technology, and these will inevitably end up being utilized and incorporated into clinical research.

Sergio Armani, vice president for business development, North America, with Advarra and ABoT member: Coming into the clinical research space as a "second career" after 22 years in financial services, I needed to keep an open mind, raise my hand to volunteer for as many

assignments as I could handle and be willing to learn as much as I can. This has allowed me to learn about clinical operations, regulatory and clinical research technology, and how they all come together to ensure that clinical trials run as efficiently as possible. Most of all though, I have searched out organizations whose mission and vision matched my own set of values, and this has helped me to work with and for some great people that will always be in my network.

Shay Brill, MT(ASCP), PMP, CCRA, FACRP, a clinical research consultant and former vice president of operations with the Atlantic Research Group: In the recent months, we all faced COVID-19 changes that were unchartered waters for the clinical trial industry. By demonstrating the following, individuals and teams benefited from this type of interaction:

- Handling stressful situations
- Taking charge in helping your team achieve their goals
- Creating environments that allow teams to thrive

I know when I've been able to do this, without being asked, I've found myself being in a position for new career opportunities.

David J. Morin, MD, FACP, CPI, FACRP, director of research with Holston Medical Group Sites and ABoT Treasurer for 2020: It’s great to have role models and mentors. I was fortunate to have both while in med school and residency, which started me on a career path in clinical research. I suggest that those who are interested in being a principal investigator (PI):

1. Start out as a sub-investigator to gain experience. Find a good mentor.
2. Remain scientifically curious and motivated to learn about the process.
3. Have realistic expectations of your responsibilities as a PI.
4. Find the time to fulfill your obligations to the research process.
5. Surround yourself with well-trained and knowledgeable research staff.

6. Stay involved with the research community, such as through ACRP and working toward certification.
7. Understand that you are doing something noble. The medical impact of a new therapy may improve the lives of many thousands.
8. Teach others and remain a positive role model.

Kelly Cairns, MA, BASc, APMR, CCRA, FACRP, leader of clinical operations and business support with Boehringer Ingelheim (Canada) Ltd./Ltée and member of the Academy Board: Someone once told me that one of the key abilities of a good, effective leader is the ability to develop their staff in order to best prepare the organization for the future. Throughout my career, my success as a leader can be measured by the success of my team. Over the years my team members have been able to grow and develop and succeed in new roles, and I have played a key role in facilitating this. In addition, whether you are preparing for a new role within your department, your organization, or within another organization, always be open to new learning and ideas as this will take you far!

Anne Blanchard adds these thoughts: It is ok to slow down and rethink process and procedures to make improvements on the go as you implement studies or organize teams. Audits and inspections (and even monitoring) are a great opportunity to test collaborations and joint work. Make sure you grow from those experiences.

Keep your eyes and ears open for continuous improvement—it is an attitude and a duty in an ever-changing environment to make the best of work and the best of all professionals working with you in the projects.

I have learned to build trust in my team, my clinical sites, and my coordinators and fellow clinical research professionals around me by learning, by teaching, by listening, and by being there for them to go through studies together one step at a time. This is probably my biggest success in my career and my asset for life.

Elisa Cascade, MBA, executive vice president and product line executive, eCOA, at ERT and ABoT member: When an opportunity to work on a special assignment arises, take it. In addition to expanding your skill set you will gain visibility to a broader network of people, which in turn may open the door to new career options.

Jennifer Byrne, CEO of Javara Inc. and ABoT member: Do not, under any circumstances, say "Yes" when you actually mean "No." Find your North Star and stick to it; don't lose that focus in terms of your own career journey. Pay attention to those smart people around you who are generously offering mentorship. The best mentors don't show up to pat you on the back, but rather they will push you to your own boundaries of discomfort and growth. Pay it forward; one good deed gifted to you requires you to pay it forward.

Wake up every day that you have the privilege to contribute to public health through your clinical research career, grateful and mindful of that responsibility that you have ultimately to the patient (that patient/person might one day be a family member, friend, or you).

Virginia Nido, global head, product development industry collaborations, diversity and inclusion sponsor, South San Francisco PD site head, Genentech, a member of the Roche Group, and ABoT member: The best career advice I've ever received is "Have six months' worth of emergency cash." The reason this is important is that no job is sacred or permanent and guess what, your company doesn't love you. You have to look out for yourself. Don't put yourself in a position that you are so cash-strapped that if you get laid off, you *have* to take the next thing that's available. Give yourself the monetary cushion so that you can take your time, think about what you want to do next, and activate your network to help you find your next role.

Deb Driscoll, vice president quality assurance, Merck Research Labs and ABoT member: From my experience, there is not one standard approach to succeeding in the clinical research field. In fact, many of us got to where we are today by pursuing unconventional or unexpected opportunities. Be open to career advice and to seizing opportunities, moving outside your comfort zone, and forging your own path.

Joy Frestedt, PhD, CPI, RAC, FRAPS, FACRP, president and CEO of Frestedt Inc.: Become an expert on "selling" the work you have already done and the work you wish to do in the future (e.g., do not under emphasize what you know)—be able to speak about it plainly and clearly, but do not oversell how little you know. People appreciate clear and honest truth.

Learn about the "work" you wish to do (e.g., talk to lots of people, do volunteer projects)—step up and ask for opportunities to help others, but do no overcommit and under deliver. People remember those who over deliver on promises.

Study your craft (e.g., take classes, attend workshops)—talk to instructors and classmates about the contents of the class, but do not waste time for busy people. People congregate with those who ask insightful questions and have an obvious interest in the subject matter.

Barbara Schliebe, MS, CCRA, CCRC, FACRP, Chair of the Academy Board: Regardless of where you are in your career, it has to be fun! If it is not fun, then move onto something that is fun, and you will be more dedicated to the position and be a better contributor.

Jeri Burr, RN-BC, MS, CCRC, FACRP, executive director of the Utah Trial Innovation Center: Over the years I've learned not to sweat the small stuff, because ours is an industry that can be quite complex with many moving parts. I have a plaque in my office that says, "In a world where you can be anything, be kind." This core value helps in building relationships and investing in making things better. It must be safe for everyone to offer their ideas. Creating the kind of culture everyone on the team wants to be in lends to a more productive workforce.

ACRP

Clinical Researcher—November 2020 (Volume 34, Issue 9)

SPECIAL FEATURE

Career Advice from Research Veterans, Part 2: Finding Meaning in the Mission

Collected by Gary W. Cramer, Managing Editor

In some professions, it is a point of pride to keep one's "secret to success" to oneself, as there are corporate ladders to climb, intellectual properties to protect, and outsized reputations to maintain. Not so in the clinical research profession, where sharing advice, lessons learned, and best practices with one's colleagues—whether through formal mentorships and training, informal networking, standard operating procedures, or other avenues—is typically done with a spirit of generosity and the goal of making clinical trials more efficient and effective for everyone, everywhere within and across organizations and national boundaries.

This being the case, it was no surprise that when the call went out for research veterans to offer up their best career advice to the readers of *Clinical Researcher,* a welcome variety of volunteers came through with flying colors, as you will see in the commentaries that follow.

Getting it Right from the Start

Like many of us who started in research, I kind of "fell into it." I started as a back office medical assistant at a practice that did studies and became a coordinator; I had no idea that role even existed! I then became a Certified Clinical Research Coordinator (CCRC) through ACRP in 2003. From there I traveled through other roles to become a Certified Clinical Research Associate (CCRA) and now have the ACRP-PM subspecialty certification in project management as well. Over the last year, I have also had the privilege of volunteering as an ACRP subject matter expert for some review activities.

Twenty years in and I could not be more proud and happy that I found such a rewarding career!

The biggest challenges I hear about involve either how to enter the field or how to move between roles (CRC to CRA), institutions (site to sponsor), or advancement levels (Senior CRA to PM).

Here are my thoughts on these challenges:

- Learn about all the roles that exist within the clinical research realm: Regulatory, Compliance, Quality, Data Management, Research and Development. You may find another area even more rewarding and exciting that speaks to your specific strengths and interests.
- An advanced degree is usually mandatory—even when you already have experience.
- Network, network, network! Did I say network? Not only does it help with professional development, but you will have connections who understand all those acronyms your family members are still confused with—you know, the SOPs, SIVs, CSRs, PMAs, and all the rest.
- Take on "stretch goals" and assignments.
    - Do you have a process improvement idea? Discuss it with your leadership and ask if you can work on it and then offer endpoints that can be used to evaluate why your idea is awesome and demonstrate success.

    - Ask your manager if he or she has some task they have just not gotten to yet that you can help with. Yes, you are probably already drowning in your own work, but if you can make time, this can give you an opportunity to demonstrate what you can do outside your usual tasks.
- Think about how you are perceived by your leadership, your image, and how to increase the visibility of what you do. Seek out assignments that allow you to be seen by others in your organization (i.e., offer to lead study team meetings, etc).
- Track your accomplishments each year and report them on your performance evaluations. No one is a better advocate for you than YOU!
    - You probably have more demonstrated successes than you realize. Did you get noncompliant patients to start making their study visits regularly? Did you have no monitoring visit findings? Did you get sites activated ahead of schedule? Did you earn any certifications or professional recognition from outside your work? Document everything!
- Maintain awareness of current trends and terms through business literature, professional organizations, and continuing education opportunities. Our research landscape is constantly changing, and we have to pivot constantly to meet the demands of leadership.
    - For example: We are now seeing a very siloed approach to sponsor CRA activities that are incorporating “agile” or “lean” methodologies. Key performance indicators and key performance metrics are what management look for, and study team members all need to be aware of what contributes to those.

It is wonderful that we live in a time where clinical research programs are now becoming a standard part of certification and degree programs. I still have much to learn or apply. There will be challenges, but loving clinical research is my foundation and I believe that if you love your career and work at it, excellence will come!

Laura Menck, CCRA, ACRP-PM, is Senior Manager of Clinical Operations at Philips.

Opportunity Knocks More Than Once

A delightful opportunity leapt out from the university newspaper when I was a graduate school student in the form of the chance to participate in Phase Ia and Ib clinical trials as a "healthy normal." Soon thereafter, I entered two trials. The first one required a three-day inpatient stay at a dedicated Phase I wing while the second one was an outpatient trial that required pulmonary function tests.

It's the outpatient trial that changed the trajectory of my career. There was something about the process that drew me immediately. The informed consent, the clear explanations of what I could expect at each step of the process, the incredible customer service of the study coordinator, and the scientific greatness of research design spoke to me 17 years ago like they speak to me now.

I was already pursuing a PhD with the intention of conducting research, and my focus was health psychology. This all felt exceedingly aligned with medical research, so I quit my get-through-grad-school job to become a study coordinator, and thus began my career in clinical research!

I continued with my degree, but found a home in medical research—first in pediatric oncology and then in orthopedic surgery at a large academic medical center (AMC), and later transitioned to a small, independent research site that (at the time) conducted infectious disease and pulmonology trials.

If a person falls in love with research, there is a place for that person *anywhere* in this amazing industry! My experience at an AMC was vastly different from my experience at an independent site in so many ways—and I adored them both. Anyplace where the investigators are passionate about clinical research is a great place to be, and I'm sure you can imagine how deeply that passion is held in pediatric oncology, where "mission driven" isn't a slogan, but a way of life.

That noted, I happen to thrive in fast-paced environments that offer significant change, and so a growth company became my career niche. Instability is frightening, but there are enormous

growth opportunities at a young or growing company. Those companies are also very likely to be understaffed at times and require people to carry high workloads.

My point is: Consider what you love. There is no right or wrong answer. What I would advise people new to the field is to discuss their strengths and the activities that give them passion with someone else in the field to see what the best fit might be. Consider what speed you like to work at, how you feel about change, whether you enjoy the opportunities that come with being part of an established company or a startup, and what type of mission most speaks to your heart.

I sincerely believe that anyone can succeed in this complicated and fascinating industry if they find an organization aligned with their strengths—and the fact is, we all need you. As an industry, we are millions strong—and that's not enough.

Christine Senn, PhD, CCRC, CPI, ACRP-CP, FACRP, CSM, is Chief Implementation and Operations Officer with IACT Health and a member of the ACRP Association Board of Trustees.

The Power of Perseverance

My introduction to the field of clinical research was not unique; many colleagues of my generation shared the same challenging circumstance. We were research-naïve medical professionals who unintentionally "fell" into our positions and experienced a trial by fire assimilation to the field. The only positive aspect of this otherwise unfortunate learning process was that it forced a pivotal decision that, once made, could only be sustained by a specific trait. This trait is what truly defines a successful clinical researcher, above all else. Perseverance.

Perseverance sustained me through the enormous stress of having to learn a new position (as a study coordinator) and a new industry. Perseverance broadened my focus beyond peripheral error to the resulting knowledge that would elevate my abilities. Perseverance, and the pursuit of

knowledge, eliminated ego and drove my requests for help in learning my position, forming lasting friendships in the process.

Three simple words define the narrative of perseverance. NEVER GIVE UP! The critical trait required to succeed in this industry is captured in a short piece of advice: If you persevere, you will succeed.

I began to understand the incredible force of this quality after I suddenly found myself working as a new clinical research coordinator (CRC). In the space of a morning, I had walked into a large health center to apply for a nursing position and was convinced by a recruiter to apply for a CRC position. In an eight-hour period I interviewed and was offered the exciting job, understanding neither how it happened nor what it was, exactly.

Over the next seven days I walked into an office stacked with case report forms and studies that lay untouched for weeks. There was so much uncollected data, patients lost to follow up, new patients to consent, and volumes of knowledge to learn. It was a time fraught with anxiety and feelings of helplessness over all I had to learn and do.

I lost count of how many times I nearly gave up and left that position. My ear ached from the barrage of phone calls from my mother ordering me not to quit. My muscles ached from tension and my spirits sagged from insomnia. It sometimes felt that I had failed for even entertaining thoughts of defeat, but then—slowly, surely—perseverance wrought clarity...clarity wrought confidence...and confidence begat stability.

At length, I understood the inclusion exclusion criteria. The queries written by my visiting monitor were not completely nonsensical. The lab manual instructions for packaging samples did not take two hours to decipher. I completed things efficiently and felt immensely gratified over job performance. This banished the once beguiling desire to give up.

I credit my staying power to the monitors who carried me, to the friends/family who encouraged me, and to the principal investigator who believed in me. Our support systems are integral to our survival, as is our ability to persevere despite self-doubt.

The best career advice I could give a new clinical researcher is twofold: No matter how difficult, stay the course to your goals, and seek out mentors to guide your career journey. Their personal experiences will remind you that you are not alone in your struggle, and that with perseverance, they succeeded, and you will too.

The best example of the impact of perseverance on a fledgling career involves a CRC with whom I worked several years ago. She was a site manager for a physician practice with a robust research department. She had worked on the investigational site side for 12 years and was determined to make the move to the clinical research industry side. She had extensive clinical training experience, with the duality of both hospital and investigational trial presentation experience. We met during a monitoring visit, where she first approached me about becoming a clinical trainer. I encouraged her to update her CV with all recent/relevant training experience and to start the application process. She was extremely diligent and passionate in her quest; as a result, she applied to dozens of companies and positions. Unfortunately, after six months she still had not received any substantial interest. However, I really admired her perseverance, her constant refusal to be deterred by the proverbial silent response to her attempts to find a position.

After a long period, she finally received an interview request for a training position. Part of the interview process included the creation of a specific PowerPoint presentation to demonstrate an adept public speaking process and content creation. Her presentation and interview were received well, and she was one of two final candidates considered for the position. Unfortunately, the other candidate was chosen. She allowed herself one minute of remorse/"woe is me" self-pity, and then she dusted herself off and jumped back on the proverbial application horse. She refused to give up on her goal. Three months later, the recruiter for the research organization with whom she had interviewed contacted her with fabulous news. She had presented so well during the interview that they had kept her CV at the top of the stack, with the intent to offer her the next open training position. She started the position two weeks later.

Talent alone will not sustain without the perseverance to ride the storm.

Elizabeth Weeks-Rowe, LVN, CCRA, is a former CRC who now works in site selection and education in the contract research organization industry.

Expect the Unexpected

As an oncology nurse, I can honestly say I never thought I would end up working for an employer outside the traditional healthcare system. Here's how it went down:

After working in a stem cell transplant/oncology ICU and then with an outpatient oncology private practice, a physician colleague asked me if I would be interested in becoming a clinical research nurse for an academic medical center's early-phase oncology program. I knew private practice infusion was not for me, so I took the leap without really knowing what the role was.

It turns out that this role was what I had envisioned when I went to nursing school; focusing on a smaller group of patients, having the time to do real nursing care, and being on the forefront of oncology treatments. The highs were telling patients who had lost hope that the novel agents were working and being part of the precision medicine movement (and away from trial and error). The lows were when patients came to us too late, as they didn't know about clinical trials.

I quickly advanced in my career and went down the administrative path. My mentor suggested I get my masters (good suggestion), so I did that in healthcare administration. I worked my way up to being the director of a dedicated early-phase oncology program within a large community hospital system.

I still saw myself as a nurse, as I was now empowering the team to help our patients. The highs were, again, giving patients hope when they didn't have any and growing the program exponentially. I adored my colleagues. The lows were the challenges of competing for resources within the hospital system. Eventually, I no longer had the fight in me, and I knew the team and our patients deserved better. I quit my job without having another one lined up.

As I was transitioning my role and informing external colleagues of my departure, opportunities for clinical research and healthcare consulting fell into my lap. One of the opportunities was to start the clinical research consulting division at a staffing company. Again, I took the leap as I found synergies with the company's purpose and the surrounding team.

In between consulting jobs, I joined meetings with the sales team to share with other site directors how I navigated both the hospital and clinical trial ecosystems. My new employer encouraged me to get involved with professional organizations to understand and create solutions on workforce issues at the industry level. Highs: I'm now helping patients on a national level by helping site leaders. Lows: I no longer get to use my epic IV skills.

My advice to those wanting to get into the industry is to network, invest in yourself (get that certification, next degree, and go to conferences), take the time to mentor others, and be open to new opportunities—even ones you never thought of to begin with.

Molly Downhour, MHA, BSN, NEA-BC, OCN, CCRC, is Executive Director Clinical Research with Medix.

Now That You've Had Some Time to Think About It…

Assuming that a portion of you reading are or have been employed in the clinical research profession for some time, but are looking for opportunities to make that "next step" in your career, I'll offer the following insights as to how I was able to advance my own career.

I always like to start with the topic of "Remember When Research was Fun?" Well, I do remember, but I also remember when it wasn't fun—times when sharing my ideas or being resourced appropriately for solutions was out of the question. By adopting a mixed methods approach—partially one that is familiar to all of us in this field (the "scientific method"), and partially one that is quite unfamiliar in our field (the "entrepreneurial mindset")—I've been able to formulate an adaptable set of practices that not only advance the clinical research effort, but my career as well!

Basically, your goal should be to seek to be a solutions-minded professional. Sure, the clinical research engine chugs forward and we enjoy myriad successes, but don't you agree that we aren't moving swiftly enough? There simply are not enough treatments and cures available for

the full effective maintenance of health, wellness, nor the common and rare illnesses with which we struggle. We need to do more, and we need to do it more efficiently.

You have great ideas. Put them to work and you will benefit science, society, and yourself—both in terms of your health and in your career pursuits.

To effect true impact, you'll need to master a few basic business principles. Here are a couple of key tools to incorporate into your day-to-day tasks to differentiate you from your peers and colleagues, and to help you advance your career objectives while also advancing the scientific endeavor:

- *Sharpen your inquisitive nature*. Incorporate critical thinking skills into every discussion and encounter. Question absolutely everything. Ask why we do what we do, and why we do it the way we do it. Then think through the details of how we can do it differently or better.
- *When attending a talk or presentation, don't simply soak it all in like a sponge*. Reach out to the speaker(s). Inquire about their tips and tricks. You'd be surprised at how engaging the experts can be—apparently, they love to share what they know (they took the time to give a talk, after all). Introduce yourself, let them know what takeaways are of value to you, then request some advice on a practical application for a matter you've been managing. The simplest outcome will be you've made a connection, and we cannot underestimate the value of networking. On the other hand, you may walk away with a keystone to turning the corner on some challenge you're experiencing in your own workplace. This also lets your bosses know that sending to you to the conference was not in vain.
- *Read the book, "How to Lie with Statistics" by Darrell Huff*. Though written more than half a century ago, the principles are still applicable to today. Now, am I saying that YOU should use statistics to lie? Absolutely not! Instead, you'll gain insights as to how data can be presented to say whatever you want it to say. This benefits you in two ways—you'll be able to critically evaluate data that are being presented to you for consumption,

and you'll obtain the foundational ability of skillful presentation of persuasive arguments that support your drive for solutions.

- *Because we all agree that timelines are a grind, I also advise emerging leaders to take a course on project management*. You'll find that the higher up the ladder you go, the more complex the operational and administrative functions will fall under your purview. When you are equipped with the tools to target key outcomes and the ability to identify what's on track versus off track with ease, you can take on more responsibility and make it look seamless.
- *Metrics and money matter*. For most in the healthcare and science arena, familiarity with finance is not a strong suit, but this is a muscle you MUST develop. The growth of the entire enterprise of healthcare delivery, including pharmaceutical manufacturing and the future wellbeing of the biotechnology sector, requires that you adopt a mindset of "dollars as drivers." Monetize it all, because without the funding, we will not have the resources (people, payroll, equipment, infrastructure) to continue to find future treatments and cures.
- *Finally, learn the language of systems and technology*. Talk technology like it's your native tongue. Simply adopt a systematic commitment to improving your own ability to transcend the language limitations brought about by the siloing of the clinical research components. Create a common glossary so you can act as a communication hub for the various counterparts across the continuum to meet the challenges of collaboration.

By incorporating one or more of the above pointers into your own approach to problem solving, you will surely be able to push the dial and present yourself as one who is poised for career advancement when the window of opportunity opens.

Good luck to you. You've got this!

Jeanie Magdalena Gatewood, MBA, is a Clinical Research Solutions Expert and Independent Contractor/Consultant with Gatewood Life Science Consulting and former Vice President Research Strategy for the Fox Chase Cancer Center.

Look Before You Leap: A Quick Framework for Evaluating Career-Related Decisions

We all, from time to time, get faced with choices involving our careers. Whether you are presented with an unsolicited job opportunity, a problem your entrepreneurial spirit wants to take on, an offer to sit on a board of directors, a change in your current workplace, or even just reevaluating your current job because your life situation has changed, you constantly need to make choices (or reaffirm your current choices) along your career's lifespan.

Anxiety from evaluating such decisions is usually alleviated by providing some sort of structured evaluation. For me, I focus on the following five variables to bring structure to my career-related decisions. They are not in order of importance, but are equal variables of how my wants and needs change congruent with my evolving life.

Autonomy: This can be evaluated on a micro and macro level. An example of a micro level is how much will you be in charge of your daily schedule while an example on a macro level may be discretion and flexibility in budgeted funds. Arguably nobody wants to be hovered over or hindered by others, but the reality is that nobody is completely free from accountability checks and/or interdependence. Essentially it boils down to under what circumstances do you believe you are ready, willing, and able to self-govern and is that consistent with the processes, key persons, and/or available resources given to you in those circumstances. Perhaps early in a career, role, or task you are more tolerant in having less autonomy (or even prefer it because of the value such collaborations may bring). Perhaps you have become less tolerant in certain situations that you experience as "big company logic," incessant "mother-may-I"s, or the "constantly looking over your shoulder" feeling. Clearly everyone is not completely free from accountability or interdependence, so when supervision and/or collaboration is required, do those people or processes that fill those roles enhance or hinder your ability to be successful?

Challenge: What will be the short- and long-term challenges you are expecting and are they at the right level for your knowledge, skills, and abilities? Will you be more under-challenged than you desire? Will you be able to handle the stress when over-challenged? When will today's

exciting challenge become a mundane task and will there be opportunities for new stimulation, learning, and reward? When do you prefer (or need) to explore and grow outside your comfort zone versus when do you thrive in getting better and better at a specific task? Preventing burnout and distractions is an ongoing process, and ultimately you need to know thyself and what will perpetually drive you.

Compensation: Clearly compensation is important, but your needs will likely change over time. Perhaps early in your career this is weighed with more importance than other variables because you are starting a family, but you may get to the point where you have adequate resources (i.e., money to live, health insurance through a spouse, etc.) to give up the steady income job to take a shot at a high-risk/high-reward opportunity. Perhaps the opposite is true, and you would prefer a more adventurous lifestyle in your youthful years to explore the world and want to deal with financial security later. You may view a matching 401(k) plan differently in your 20s, 40s, and 60s. It's also not only about money but the non-monetary compensation. When will you be using all those perks (e.g., the onsite gym, the company wellness program, etc.)?

Legacy: When you look back at your day/month/year/career, what will live on because you did what you did and how important is that to you? Are you content living on in the memories of patients and families as the one who helped them personally, or do you want to accomplish other things? Do you want to use your abilities to make fundamental changes to industry practices? Do you have the burning desire to pay it forward to the next generation of professionals by helping them be successful? When looking at this variable, you have to first reflect and decide on what you want to leave behind in your wake and then ascertain if the opportunity you are evaluating gives you the platform and/or resources you need to achieve it.

Lifestyle: There are tangible and intangible factors to consider with regard to lifestyle. The flexibility between work and non-work life obligations is usually the key focus. This may be acutely influenced if you have others who are dependent on you or when you have core values you are not willing to compromise. What is the expected fluidity between work and non-work obligations when needed (i.e., can you take care of your personal obligation(s) arising during traditional working hours while tolerating the expected workload needed outside those hours)? Is the daily commute tolerable? Will you have to relocate, and if so, when or how often? When will

travel requirements be a positive and when will they be a negative? To what extent might you be able to enhance any of your political/religious/family/health/personal values and activities, or will any of these demand unacceptable compromise? You are not your job, but a complex person with complex wants and needs, so how will the opportunity help or hinder you?

For a final note, whatever and however many variables you decide on as your evaluation criteria, it may be helpful to determine some sort of professional creed or mission as a quick test. For me, I developed "to make our data a little better, our research subjects a little better off, and our workday a little easier" as my quick test to see if adding or subtracting something from my career is worth my time and effort. After all, I am trading an hour/day/year/etc. of my life for it, so I should be selective in what I do.

Hopefully, you will thoughtfully create a decision paradigm that can evolve over time and that will help you drive your career decisions to meet your overall life goals. I know I have.

David Vulcano, LCSW, MBA, CIP, RAP, ACRP-CP, FACRP, is Vice President and Responsible Executive for Clinical Research at HCA Healthcare.

Reflections on Research in the Rearview Mirror

After 30 years in nursing and 12 years of conducting dermatology trials, I only wish that I had found this niche in the field of nursing sooner. The beginning was tough. It was a different language. 1572s, CRAs, SIVs, SAEs…WHAT DOES IT ALL MEAN? I was a seasoned nurse who felt like a new graduate.

The principal investigator (PI) wanted one full-time research nurse. I convinced him to hire two part-time nurses. Although compensation package costs for two people were a concern, the PI quickly realized the benefits far outweighed any additional costs. As it happened, my work partner and I both declined health insurance in lieu of our spouses'

coverages—we were part-time nurses and full-time moms. We had flexibility to accommodate our subjects while simultaneously balancing our family lives.

The biggest benefit to the PI was that we covered for each other; he was never troubled with life's daily challenges. We brainstormed equitable solutions and one of us was always there to get the job done. We were a two-nurse show for many years. We did the institutional review board submissions, marketing, source documents, scheduling, EKGs, blood draws, and lab processing. You name it, we did it.

When I met a brand new research nurse in another department, I empathized with the bewildered look on her face. That was my expression in the early days. I could only tell her that it would get easier and that I had dry ice she could borrow anytime. It was my job to learn a subject's entire medical history. I bonded with my subjects and this translated into exceptional protocol visit compliance. Rarely did I have a subject miss a visit. I decided to become a Certified Clinical Research Coordinator (CCRC) through ACRP. Being a nurse and having real experience in research gave me a great foundation for passing the exam. I'm proud to have the CCRC designation after my name.

As for tips to consider, let me start by saying that an outstanding research assistant is a true asset. I used to assume that any nurse would be a great research assistant, but unfortunately learned the error of my ways though a few hires who did not work out. Take time to find a qualified, detail-oriented person to do research. Create a test. Dictate numbers for the person to transcribe. Have them answer basic math problems. Don't be blinded by credentials.

Stick to your ethics. If something is not right, speak up. Advocate for your subjects. I was fortunate to work with a wonderful, ethical PI. However, you must always be ready to speak up if the protocol isn't being followed or if a subject's rights aren't being protected. Take the consent process seriously. There are exactly ZERO shortcuts for consent.

Include every research study that you participate in on your CV. Recruiters value this information. Take credit for what you have contributed to science. Research is a truly rewarding career. There is nothing like see a drug commercial on television and knowing that you provided

quality data for that drug's approval. It's a wonderful feeling to help people.

My department decided to terminate research when the PI retired. It was heartbreaking. There were good studies in the pipeline and the world's best research assistant was fully trained. She easily transferred to another research department within my organization.

As for me, I'm in limbo. My research responsibilities have been replaced with other obligations. In my personal life, my daughter was diagnosed with type 1 diabetes. I wonder if this is my signal to move into diabetes research. Insulet? Dexcom? Eli Lilly? I love you for giving my daughter a normal life. Call me! I'm on LinkedIn.

Danica Uzelac RN, BSN, CCRC, is Clinical Research and Photopheresis Programs Coordinator with the Rush University Medical Center.

In Parting: A Visit and Lessons from ol' Research Nurse Joy
(With inspiration from Clement Clark Moore's *A Visit from St. Nicolas*.)

Twas the night before due date and scrambling about
Knowing I had to tell tales to those just starting out;
My career has been long and positions not few,
And because of this here are my lessons to you;
Whether starting anew or changing mid-view,
Stay true to yourself whatever you do;
Become smart through self-learning or classes or view,
The information available on the worldwide web for you;
If research is new don't give it a thought,
Many have been in your shoes and tripped quite a lot;
Rely on the experts those folks at A-C-R-P,
And think of research as a new recipe;
One of protections of people who care enough to be,
Enrolled in something so new you'll be there for Side A and Side B;
Protecting those folks will become the job of your core,
While following all the regs from those agencies we adore;
Oh, and just when you think you have all them down pat,
A new study set up comes through, like Virtual, and gets on your back;
Believe in yourself and stand by your goals,
Those important promises you make to yourself as you doze;
Write blogs, publish papers, give lectures galore,
Collaborate with work mates, join committees, share your knowledge some more;

Don’t keep it to yourself, share your newfound smarts with all,
And volunteer! Volunteer! Volunteer cause it’s a ball;
Spend time for yourself in this whirlwind career,
Knowing some days, it will feel like you’ve been kicked in the rear;
Get certification as soon as you are able to,
Cause obtaining your certs is the professional thing to do;
And while all this knowledge is stirring you around,
Decide to get serious and write something down;
Share experiences you have because none are the same,
Because sharing helps bring you closer to your A-game;
Breathe deeply when stress and worry are making you blue,
And cherish those mentors and leaders and crew;
Because often they show up all shiny and bright,
Taking you out of what you thought to be only the night;
Then after that breath, take on a new challenge or two,
God knows I’ve been challenged a bad time or two;
Keep your eye on your prize, whatever it may be,
And smile and give it back to those lower than thee;
Be kind to those also who are busier than you,
While offering a hand or to cover a visit or two;
Cause working together can be few and far between,
Set an example for others no matter how keen;
I’ll not say it’s easy and you might lose your way,
By mistakes or by staying with a job that has swayed;
Stay true to yourself for the times now and then,
When your tears or your heartache seem never to end;
This career path you’ve chosen can cause bumps, bites, and falls,
But in the end, it’s about cures from those diseases and all;
So as pandemic and solitude keep all far away,
Breathe deeply again and continue your day;
To fight the good fight for those who can’t or are sick,
Helping find the right new thing that could do just the trick;
Knowing research is the career path you’ve chosen and then,
One that takes you to a retirement with fulfillment and Zen;
To a time when you’re grateful for those bumps, bites, and falls;
To have kept your humor, autonomy, beneficence, and justice for all!

Joy Jurnack, RN, CCRC, CIP, FACRP, is a research nurse in CKD and Treasurer of the Academy of Clinical Research Professionals.

ACRP

Clinical Researcher—November 2020 (Volume 34, Issue 9)

GOOD MANAGEMENT PRACTICE

Clinical Research Systems and ROI: Cumulative Burdens Tip the Scales in Favor of Integration

Erin L. Pennington

Clinical trial management systems (CTMSs) and electronic institutional review board (eIRB) systems have been staples in the information technology (IT) landscape of research organizations and supporting the operations for clinical trials and local IRB offices for more than a decade. Despite the evident overlap of data fields, many organizations lack meaningful integration between the two and still question the potential return on investment (ROI) for pursuing such integration. As electronic regulatory (eRegulatory) systems grow in popularity, even those organizations with some level of IRB and CTMS integration may find themselves reconsidering their approach, especially as funding and resources tighten in response to the COVID-19 pandemic.

It's important to note that while most of the top commercially available CTMS and IRB systems support at least some level of integration, if your current systems are home-grown, outdated, or highly customized, additional discussions may be needed with your IT professionals and vendors to assess technical capabilities and determine if upgrades or modernization efforts may be required first.

Where to Begin?

Historically, many organizations have abandoned integration plans because the appropriate directional flow of data was unclear. For example, should the CTMS feed the IRB, or should the IRB feed the CTMS?

Many clinical trials will be considered at a site that may never progress beyond the proposal stage. Nevertheless, the trials are entered into CTMS to track the processing of non-disclosure agreements, feasibility/scientific committee reviews, or funding proposals. At the same time, premature submission into the eIRB system can create extraneous records, potentially impacting IRB volume and turnaround metrics.

Furthermore, not all IRB submissions should necessarily result in a CTMS record. Typically, the CTMS will contain only a portion of the research that might pass through an IRB. If one allows for direct entry into the IRB system, it is challenging to enforce entry into the CTMS without risking duplicative submissions.

There can also be financial implications for investigative sites. Many studies are needed in the CTMS for tracking purposes well before a funding source is even identified, and IRB submissions often incur fees. Many CTMS vendors use a tiered maintenance fee structure, so adding CTMS records purely as a conduit for IRB submission can unnecessarily inflate CTMS ownership costs.

Additionally, defining even simple data fields can create unforeseen challenges. For example, consider a principal investigator (PI) change on an industry-sponsored trial. Should the CTMS update the PI when the IRB approves it or when the clinical trial agreement is amended? The answer may change depending on how the CTMS is leveraged for sponsor invoicing and existing or planned integrations with electronic resource planning and grants accounting systems.

There isn’t a clear, one-size-fits-all answer.

Reasons to Persevere

With all these challenges and the need for a distinct workflow and adherence to detailed procedures related to submission, it's easy to see how organizations could conclude that pursuing integration is not worth the investment of resources. However, there is much more to the business need beyond the initial submission.

Considering that the average study goes through numerous protocol and administrative amendments, the ongoing maintenance of IRB information into the CTMS creates a significant administrative burden. There is, in fact, much to be gained by leveraging the CTMS for regulatory support:

- **Metrics tracking.** Turnaround times for regulatory submissions and approval are critical components of monitoring activation times.
- **Compliance**. CTMS features often allow for the identification of delays in amendment submissions, suspended enrollment status, outdated consent versions, and expired approvals.
- **Resource efficiency.** A central regulatory team can improve compliance and free up study coordinators to focus on study conduct. The ability to track the receipt, submission, and status of regulatory documents is vital to supporting communication between research and regulatory teams.
- **Sponsor invoicing triggers.** If the CTMS is used for sponsor invoicing, all those regulatory submissions, continuing reviews, and amendments have associated administrative fees. The CTMS is a convenient way to track this activity and ensure this revenue is captured.
- **Document and information transparency.** Provide ready access for staff outside the approved IRB research team—investigational pharmacy, clinical research associates, research cores, hospital, and financial and administrative staff.

The cumulative burdens tip the scales in favor of integration. Maintaining two systems in parallel results in considerable and wasteful efforts. Namely, the resource time needed for data entry on every staff change, amendment, continuing review, and reportable new information into both the

CTMS and the IRB system becomes excessive, as does the frustrating cycle of downloading documents from one system just to upload them into another (and the quality control mechanisms that must be implemented to ensure this manual process is executed correctly).

Organizations that also have an eRegulatory system experience even greater burdens, including maintaining iterative versions of documents that may be needed in addition to final approvals. Regulatory and research teams must keep all these systems, each with unique needs and purposes, in alignment. Yet, none of those systems, alone, perfectly addresses the challenge of getting information and study documents to the right place, at the right time, for the right people.

Support for Seamless Integration

With the arrival of the global pandemic, research organizations are facing renewed cries to do more with less. Budget constraints and hiring freezes compound the already-significant challenges of managing a remote workforce.

While the cost to implement and maintain a CTMS systems varies widely based on selected vendor and delivery model (e.g., SaaS, hosted, onsite) initial investments upwards of a million dollars are not uncommon. In comparison, the cost of web-based integrations, even fairly extensive ones, can be done for around the average annual salary of a full-time regulatory coordinator. As vendors adopt standardized integration frameworks (e.g., HL-7, IHE) these costs will likely come down.

CTMS and IRB integration can provide much-needed efficiency improvements, reduce work redundancy at investigator sites, and improve recovery of clinical trial revenue. Further integration with eRegulatory systems can facilitate remote monitoring access for sponsors, therefore avoiding potential delays in sponsor reimbursements. Set up correctly, integration between CTMS and IRB, with or without an eRegulatory system, will more than deliver a significant ROI.

Engaging with an experienced organization that knows the logistics and nuances of clinical trial administration and management can help organizations realize this ROI much more quickly.

Further, a trusted partner can help ensure each organization is not “reinventing the wheel”—especially in an environment that is so complex and driven by regulatory requirements.

Erin L. Pennington is a Director with the Huron Consulting Group in Houston, Texas, where she specializes in clinical research operations and infrastructure development and CTMS implementation and integrations.

Clinical Researcher—November 2020 (Volume 34, Issue 9)

RECRUITMENT & RETENTION

Patient-First Approach Enables Home-Based Support During Orphan and Rare Disorder Studies in Pandemic Conditions and Beyond

Donovan Quill

Thirty million Americans live with a range of 7,000 rare or orphan diseases, and while many affected patients have struggled with reduced care, isolation, and adherence issues for most of their lives, the issue of self-isolation during the COVID-19 pandemic has added to their quality-of-life challenges. These individuals now face elevated stressors due to being immunosuppressed, conscious of infection, and hypersensitive to viral threats. Orphan diseases include disorders such as Huntington's disease, amyotrophic lateral sclerosis, Cushing syndrome, Alpha-1 antitrypsin deficiency, chronic immune thrombocytopenic purpura, and muscular dystrophy.

Despite restrictions, patients continue to require a high level of therapy adherence support at a time when some pharmacies have reduced their hours. This impacts communication with physicians and other advocates at a time when patients' contact with the "outside world" has already been severely disrupted due to the need for social distancing.

Many sponsors of drug research also report that patient enrollment in clinical trials has been compromised, prompting contract research organizations and their partners to seek technology solutions that overcome the impact of the pandemic and other challenges. Tailoring information technology hardware and software solutions based upon clients' data-related needs can help to resolve these issues and improve patient engagement across multiple dimensions of research and development—from clinical trials to commercialization and compliance.

At this intersection, a patient-first approach that focuses on and customizes services for small patient populations is of high value. These targeted programs and services deliver specialized expertise beyond the scope of capabilities provided by traditional, legacy care models that are simply built for scale. As a result, applying this focused approach with a lens on orphan diseases can better address the patient-centric experiences, outcomes, and requirements of a clinical trial.

How Patient-First Impacts Clinical Trials

COVID-19 is proving to be a catalyst for improved clinical trial solutions, with study sponsors seeking to get patients into clinical trials more rapidly as a means of advancing research, especially for the new coronavirus. Generally speaking, clinical trials for other conditions struggle to continue during the COVID-19 pandemic, making it more important than ever to identify innovative ways to keep trials on track and moving forward.

During this kind of healthcare crisis, using tools that enable home-based clinical services, direct-to-patient support, and remote monitoring has become essential to keeping clinical trials running smoothly in an environment of unprecedented complications. In fact, in March 2020, the U.S. Food and Drug Administration published guidance on managing clinical trials during COVID-19, including carrying out assessments via phone or virtual visits and offering additional safety monitoring for clinical trial participants who can no longer access an investigational product or site.

As the clinical trials market continues to grow—it is projected to reach $65.2 billion by 2025 — the pandemic represents just one challenge that patients, providers, and drug manufacturers face

in the rare and orphan market. These challenges include managing the high cost of clinical trials and encouraging ongoing patient recruitment and retention in them.

As a preferred care partner for manufacturers, the patient-first methodology provides cost-effective programs and a streamlined approach that includes such financial advantages as a flat fee for services, a single source distribution (which offers more control over the patient experience), and national access. Products are properly and promptly distributed, and patient services are designed to ensure compliance and quick, accurate reimbursement processing.

For example, one pharmacy distribution and patient management organization for the treatment of orphan and rare disorders was involved in two clinical trials at the outset of the pandemic. This participation helped patients receive investigational products without going to the doctor's office with the help of telehealth to oversee the process. As a result, the trials had significantly more patients involved, despite the national lockdown, and the organization was able to ensure that patients and staff remained safe while participating in the studies.

Other Benefits of the Patient-First Strategy

With a patient-first approach, wholesale distributors, specialty pharmacies, and hub service providers are connected under a "One Stop Shop" program instead of operating independently. The continuity across the entire patient journey, beginning with clinical trials, strengthens communication, yields rich data for more informed decision making, and improves the overall patient experience.

A patient-first focus also addresses all variables around collecting data, while maintaining frequent communication with patients and their families to ensure compliance and positive outcomes. This approach benefits the sponsors of drug research by bringing continuity of care that is critically missing from the legacy care model, with a net result: patients have a better experience, which is, after all, a critical component of a product's value.

In the rare disease space, most drug manufacturers have worked with multiple specialty pharmacy partners and an internal or external product hub, but this unique patient-first approach offers key advantages:

- *Single source*—When a manufacturer uses several specialty pharmacies and a patient in clinical trials switches to the commercial drug, the payer will almost always have a distribution preference inside its network, which can force patients to change pharmacies — and potentially disrupt care. The single-pharmacy, patient-focused model finds the right drug for the patient. When there's only one place you can get this drug, it will be covered by insurance.
- *Competitive edge*—Patients with rare and orphan disorders and their physicians must overcome massive hurdles in achieving any level of consistent care. When a new therapy is available on the market, switching to a new drug can lead to physical, emotional, clinical, and economic challenges. These drugs literally can cost hundreds of thousands of dollars per patient per year, and insurance companies pay close attention to the value received for every dollar spent, prompting doctors and patients to think twice before considering a new therapy. The patient-first methodology specializes in helping patients and providers overcome this reluctance when changing drugs would improve outcomes. This provides a competitive edge in addressing clinical and insurance challenges.
- *Pharmacy pricing model*—A core difference between the legacy and patient-first model is how pharmacies are compensated. With the legacy care model, pharmacies earn a margin on the products sold as they strive to keep millions of patients compliant with maintenance medications. When the focus is on the product instead of the patient, the pharmacy's incentives can get misaligned—they're focused more on monthly profits, which can lead them to focus on how much time hub service employees spend on the phone. These incentives prevent pharmacies from being truly patient-focused and able to deliver the best possible care.

Rare and orphan disease patients require a high level of support and benefit from high-touch service. A care team, including a program manager, care coordinator, pharmacist, nurse, and specialists, is 100% dedicated to the disease state, patient community, and therapy. This is a critical differentiator from other specialty pharmacies and hub service providers, which tend to push technology solutions that fail to address human needs and variability.

Key Benefit for Sponsors

Sponsors of every size can leverage this continuity of care for a streamlined, “One Stop Shop” approach to optimize the patient journey. Furthermore, the patient-first care model has been proven with a number of programs over the past decade with improved patient outcomes, and with compliance, patient retention, patient utilization, and satisfaction rates of 90% or more for orphan and rare disease therapies (this is compared to industry standards of about 70% to 80% for specialty drugs and 50% for non-specialty drugs).

Donovan Quill is President and CEO of Optime Care in Saint Louis, Mo.

Clinical Researcher—November 2020 (Volume 34, Issue 9)

REGULATORY COMPLIANCE

How PBPK Modeling Can Replace Drug-Drug Interaction Studies

Karen Rowland Yeo, PhD

Patients often take more than one drug at a time, especially elderly patients and those with complex diseases, such as cancer and neurological disorders. Therefore, it is crucial to determine what the potential risk might be of a new drug candidate interacting with existing marketed medications.

Drug-drug interactions (DDIs) occur when two or more drugs interact with each other. Together the drugs might produce a different pharmacological or clinical response from that seen when they each act independently. DDIs can increase, decrease, or delay drug absorption or metabolism. DDIs can also increase or decrease drug action and cause adverse events. As a result, DDIs can have a significant impact on a drug's benefit-risk profile.

The U.S. Food and Drug Administration (FDA) requires that an investigational drug's clinically relevant DDIs are identified during the drug development process as part of the sponsor's assessment of the drug's benefits and risks. Those DDIs need to be defined by nonclinical and clinical methods at drug approval, monitored after approval, and communicated in the product labeling.

FDA's Approach

Underscoring the importance of this practice, the FDA states, "Unanticipated, unrecognized, or mismanaged DDIs are an important cause of morbidity and mortality associated with prescription drug use and have occasionally been the basis for withdrawal of approved drugs from the market. In some instances, understanding how to safely manage a DDI can allow approval of a drug that would otherwise have an unacceptable level of risk."{1}

Further emphasizing the regulatory significance of DDIs, the FDA published two guidance documents in January 2020—one each focusing on *in vitro*{1} and clinical{2} cytochrome P450 (CYP) enzyme- and transporter-mediated drug interactions. While these guidance documents do not cover all types of DDIs, CYP 450 enzymes contribute to about 70% of the overall metabolism of marketed drugs.

Studies to investigate CYP enzyme- and transporter-mediated DDIs need to determine:

- Whether the investigational drug alters the pharmacokinetics (PK) of other drugs (a DDI "perpetrator")
- Whether other drugs alter the PK of the investigational drug (a DDI "victim")
- Magnitude of changes in PK parameters
- Clinical significance of the observed or expected DDIs
- Appropriate management and prevention strategies for clinically significant DDIs

Other global regulatory agencies, such as the European Medicines Agency and Japan's Pharmaceuticals and Medical Devices Agency, follow a similar approach to the FDA regarding DDI guidance. Additionally, in September 2020, China's National Medical Products Administration issued its technical guidelines for drug interaction research.

Optimizing DDI Risk Management

There are several characteristics that make drugs more susceptible to clinically significant DDIs, including a narrow therapeutic index, nonlinear PK, steep dose response curves, and enzyme- or transporter-inhibiting or -inducing properties.{3}

An enormous number of drug combinations could occur in practice, so it is impractical and unethical to test for all possible DDIs in clinical studies. However, physiologically based PK (PBPK) modeling allows drug combinations to be tested using computer-generated, virtual patient populations without involving any real patients. As these models can incorporate genetic, physiological, and epidemiological data, they can also simulate patient populations with different demographics and ethnicities, and can be used to evaluate both the investigational drug's potential to be a DDI perpetrator or victim.

Regulatory Acceptance

In its aforementioned *in vitro* DDI guidance, the FDA includes more than 20 citations regarding the use of PBPK modeling to help translate *in vitro* observations into *in vivo* predictions of potential clinical DDIs. The agency reports that PBPK models can predict the DDI potential of an investigational drug and/or a metabolite as an enzyme substrate or an enzyme perpetrator.{1}

Further, in its clinical DDI guidance, the FDA states that PBPK models can be used in lieu of some prospective DDI studies. It notes that PBPK models have successfully predicted the impact of weak and moderate inhibitors on the substrates of some CYP isoforms (e.g., CYP2D6, CYP3A) and the impact of weak and moderate inducers on CYP3A substrates. Prior to using PBPK modeling, however, FDA recommends that sponsors verify their models using human PK data and information from DDI studies that used strong index perpetrators.{2}

While these final guidance documents address small molecules, roughly half of the new drugs being developed are either therapeutic proteins, combination small/large molecules, or other types of complex biologics. The FDA is addressing those DDI challenges as well, and issued a draft guidance in August 2020 that cites PBPK as an emerging approach for evaluating DDI potential in therapeutic proteins.{4}

The FDA's acceptance of PBPK modelling in lieu of clinical DDI studies has steadily evolved. Initially both inducer and inhibitor studies were needed to verify the PBPK model. Later, only one study was required. Now there are instances in which no clinical DDI studies were conducted with the drug as a victim.{5}

Case Studies

Ibrutinib

Approved for the treatment of mantle cell lymphoma, ibrutinib is susceptible to interactions with a strong inhibitor and inducer of CYP3A4 enzymes. PBPK models built using *in vitro* data were validated using clinical data on the observed effects of both a strong CYP3A4 inhibitor and a strong inducer on ibrutinib exposure. Simulations then predicted the effects of a moderate CYP3A4 inducer and other CYP3A4 inhibitors (strong, moderate, and weak) on ibrutinib exposure. They also investigated the impact of dose staggering and dose adjustment.

This example is cited by the FDA as a best practice. The final drug label featured 24 DDI claims, which were included without the need for clinical trials. It also included a dose optimization strategy for patients with different metabolic profiles.{5}

Cobimetinib

Approved for the treatment of advanced melanoma, cobimetinib is a kinase inhibitor. This case would traditionally have followed a similar PBPK modeling approach to ibrutinib, with model verification based on CYP3A4 strong inhibitor and inducer clinical data. However, with cobimetinib, which is a CYP3A4/UGT2B7 substrate, the sponsor had only itraconazole (a strong CYP3A4 inhibitor) data available and no rifampin (inducer) data.

To create the model, the itraconazole study data was combined with mass balance, human PK, and *in vitro* data to predict the inducer effects and inform the final drug label. In this instance, the PBPK simulator's oncology population file was leveraged to predict the effects of CYP3A4 modulators on cobimetinib PK in healthy volunteers and cancer patients using data from only one clinical study. The resulting inducer recommendations on the final label were informed using PBPK simulations alone.{5}

Voxelotor

Approved for the treatment of sickle cell disease (SCD), voxelotor is the first treatment that directly inhibits sickle hemoglobin polymerization, the principal cause of the condition. In this case, PBPK modeling was initially used to determine dose projections for children aged nine months to 12 years. First, a virtual SCD patient population was developed using *in vitro* and clinical data from healthy volunteers and SCD clinical studies. The resulting model was verified using voxelotor data from adults and adolescents with the disease, and then successfully employed to predict drug exposure in children.

A follow-on request was received to predict voxelotor DDIs with CYP3A4 enzymes, but there were no data from clinical DDI studies using the drug as a victim upon which to draw for building the model. In that instance, the dose prediction model built for healthy and SCD patients was leveraged, together with *in vitro* data, to create the DDI predictions. Sensitivity analyses performed under multiple scenarios were then used to inform the final label without the need for clinical studies. Furthermore, there was no post-marketing requirement for DDI studies.{5}

Conclusion

PBPK modeling is an effective, accepted method of informing and replacing DDI studies, thus saving time and money. It is a proven asset, helping to manage potential DDI risk for patients who need to take multiple medications concurrently. We anticipate that the use of PBPK modeling for assessing DDI potential will soon be expanded into other areas, such as transporters, and it will also be employed to answer many other drug development questions.

References

1. U.S. Food and Drug Administration Guidance. 2020. In Vitro Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.

2. U.S. Food and Drug Administration Guidance. 2020. Clinical Drug Interaction Studies—Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.

3. Hermann R, et al. 2018. Core Entrustable Professional Activities in Clinical Pharmacology: Pearls for Clinical Practice Drug-Drug and Food-Drug Interactions. *The Journal of Clinical Pharmacology* 58(6)704–16.

4. U.S. Food and Drug Administration Draft Guidance. 2020. Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry. https://www.fda.gov/media/140909/download

5. Yeo K. 2020. Simcyp PBPK for Drug-Drug Interactions (DDIs): A Regulatory Imperative. https://www-cdn-assets.certara.com/app/uploads/2020/09/WP_DDI-Optimized.pdf

Karen Rowland Yeo, PhD, is Senior Vice President of Client and Regulatory Strategy at Certara UK Limited's Simcyp Division. Previously, she was Head of PBPK Consultancy Services at Simcyp, leading a team of scientists applying PBPK modeling in the drug development process.