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Making an Impact in Clinical Research Early in Your Career With the DRCR.net

Since 2002, the National Eye Institute-funded Diabetic Retinopathy Clinical Research Network (DRCR.net) has made important advances in understanding diabetic retinopathy, changing the way all ophthalmologists view and treat this disease. Equally important is the Network's impact on the development of new retina clinician-scientists.

The DRCR.net has inspired and guided many early-career retina specialists to become involved in clinical trials; its open-network policy welcomes any potential investigator with an interest and strong motivation for clinical trials.

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Diabetic Retinopathy: A National Research Priority

Diabetic retinopathy is a leading cause of blindness in America. According to projections by the National Institutes of Health, the number of patients with diabetic retinopathy will nearly double from 2010 to 2050, affecting nearly 14.6 million Americans. It is therefore imperative to make combating and treating diabetic retinopathy a priority in our national research efforts.

The objective of the Diabetic Retinopathy Clinical Research Network (DRCR.net) is to develop a collaborative network to facilitate multicenter clinical research focused on diabetic retinopathy and associated conditions like diabetic macular edema (DME).

Since 2002, the DRCR.net has involved over 300 sites and 1100 investigators, spanning 48 states and 4 Canadian provinces, with nearly two-thirds of participants from private practice.

DRCR.net Chair Lee M. Jampol, MD, actively encourages the participation of young retina specialists—our specialty's future leaders. When retina specialists are just beginning to build their own practice, they "may not be maximally busy, so they have time to be involved," he explains. Dr. Jampol enjoys working with young people; it "keeps me young and maintains my mental clarity and enthusiasm," he adds.

Senior DRCR.net investigators work closely with junior investigators to train them as potential future leaders. Young investigators are regularly appointed to leadership positions, giving them invaluable experience early in their careers.

We have interviewed 4 active network leaders—retina specialists who got involved immediately after fellowship training. Jennifer Sun, MD, MPH, a former vice chair of the Network, serves as the DRCR.net protocol working investigator; she practices at Beetham Eye Institute at Joslin Diabetes Center in Boston and is an associate professor at Harvard Medical School.

Chirag Jhaveri, MD, is a Network vice chair who practices at Retina Consultants of Austin in Austin, Texas. Omar Punjabi, MD, practices at Charlotte Eye, Ear, Nose & Throat Associates, PA, in Charlotte, North Carolina and serves on the research committee of South Eastern Clinical Research Associates (SCRA), based in Charlotte, North Carolina.

Charles Wykoff, MD, PhD, is a member of the DRCR.net protocol development and writing committees and practices in Houston, Texas, as co-director of the Greater Houston Retina Research Foundation; he also serves as the deputy chair of ophthalmology for the Blanton Eye Institute.

Drs. Jhaveri, Punjabi, and Wykoff are still less than 7 years out of fellowship, so they are members of the Young Physicians Section (YPS) of the ASRS. They each provide unique insight on how their experience with the DRCR.net has helped their careers—and they share great advice on how to become a part of the Network.

How and why did you get involved in the DRCR.net?

Jennifer Sun: I got involved in the DRCR.net soon after I joined the Joslin Diabetes Center as a new attending right out of fellowship. The goals of the Network fit closely with my clinical and research interests in improving our understanding and treatment of diabetic eye disease. Lloyd Paul Aiello, MD, PhD, was my mentor at the time in the NIH-sponsored Harvard Vision Clinical Scientist K12 program; he was the founding chair of the Network, so his mentorship also played a role in fostering my involvement with the DRCR.net.

Initially I got involved by simply recruiting for the Network studies. Being a highly active recruiter is the best way to gain familiarity with the Network policies and protocols. It also leads quickly to other opportunities, such as participation on protocol development and

manuscript writing committees. Over time, I broadened my roles in the Network, having served as one of the vice chairs and as the protocol working investigator. In my current protocol role, I help shepherd all new study ideas from inception through approval, development, and implementation.

Chirag Jhaveri: I was introduced to the DRCR.net by my mentors in fellowship and by my partner in practice. I saw the Network as an excellent opportunity to participate in collaborative efforts that will likely influence the way I will manage patients with diabetic retinopathy throughout my career. In addition, the DRCR.net has been a great resource for becoming involved in clinical trials and research as a new physician.

Omar Punjabi: I had the opportunity to be exposed to research very early on in my career. During residency training at Northwestern University, I was fortunate to have worked with Lee Jampol, MD, the current chair of the DRCR.net. My retina fellowship was at the Cleveland Clinic's Cole Eye Institute, where there was a heavy emphasis on research by Chairman Daniel Martin, MD. These formative years piqued my interest in clinical research.

One of the reasons I joined Charlotte Eye Ear Nose & Throat Associates, PA (CEENTA) was because it has an established research setup, and a long history of dedication to clinical research. My retina colleagues at CEENTA have been active with the DRCR.net for several years and have served in leadership roles in the organization.

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>
> —Chirag Jhaveri, MD

Charles Wykoff: Harry Flynn, MD, a key mentor of mine as a resident and fellow, encouraged me to get involved with the DRCR.net early in my career. When I joined a retina-only practice with 10 doctors to help lead our research efforts, we had no presence in the Network, and I decided to engage our group. Involvement with the DRCR.net has proven incredibly productive and valuable.

What have you learned from participating in the DRCR.net, and how has it shaped your career?

Jennifer Sun: I have learned a tremendous amount from my co-investigators and from working with the Network coordinating center. The open discussions in the DRCR.net have helped me learn how to design clinical studies and how to evaluate clinical research thoughtfully. As a young investigator, I have had a great opportunity for ready access to experts in the field.

It has also been very exciting to be involved in an organization that has dramatically changed best practices for management of diabetic retinopathy and DME over the last few years. Being a DRCR.net investigator gave me early access to and a deeper understanding of results from clinical trials that established anti-VEGF therapy as first-line treatment for DME and as a safe, effective therapy for proliferative diabetic retinopathy (PDR).

Chirag Jhaveri: Because the DRCR.net is an open network, it is an excellent tool to learn how complex multicenter trials are planned and implemented. From the beginning, the team at the Jaeb Center for Health Research, the Network's coordinating center, is extremely helpful for a new clinician wanting to understand the steps required to participate in a clinical trial.

As I became more involved, I was not only learning; I also was able to participate in the decision making for protocol development. At DRCR.net meetings, there is a collaborative discussion when new protocols are being considered, and it's a great opportunity to brainstorm with your colleagues. This open and collective effort is what I think makes the DRCR.net special.

Omar Punjabi: The first few years as a retina specialist involve a lot of hard work, patience, and flexibility. I trained in a very busy fellowship program, but there was still a very steep learning curve during my first few years in practice. It can be hard to find time for research.

I tried to get involved in research from day one. I keep a summary of ongoing clinical trials (key inclusion and exclusion criteria, protocol schedules, etc), and have it handy in each clinic lane. This allows me to quickly determine if a patient is eligible for clinical trials. Research patients now encompass approximately 10% of my patient volume.

Since we are involved in all the DRCR.net trials, I have learned how research studies are formulated and how inclusion and exclusion criteria are used to determine subject eligibility. Understanding how clinical trials are structured has also helped me fine-tune my treatment algorithm for some retinal diseases.

The Network recognizes sites and investigators who recruit heavily, and we were thrilled when our site was named the 2015 DRCR.net Site of the Year. The DRCR.net invites sites that are heavily involved in recruitment to important meetings and to serve in larger roles within the organization.

The DRCR.net provides us with financially unbiased scientific data that helps us treat patients better, and become better doctors. I feel like I have improved a lot as a physician by being part of the DRCR.net.

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>
> —Omar S. Punjabi, MD

Dr. Wykoff: Before starting practice, I had substantial experience with basic science research and single-center studies, but had little exposure to large, prospective clinical trials. That changed rapidly after joining the DRCR.net. There are many steps to a successful prospective study, including trial design; institutional review board (IRB), Food and Drug Administration (FDA), and industry interaction; consenting and educating patients; data collection; and data analysis. Every step is vital and unique, involving complementary skill sets.

Beyond learning the nuts and bolts of trials, there are innumerable benefits to embracing the world of clinical research and participating with the DRCR.net. The relationships built with collaborators across the country and around the world have spawned multiple subsequent projects. It's motivating to collaborate with retina colleagues similarly dedicated to pursuing a deeper understanding of retinal diseases and their management.

What are the pros and cons of being a part of a multicenter clinical trial investigation?

Jennifer Sun: One of the pros of being part of a multicenter clinical trial investigation is that you immediately have access to protocols and procedures designed by leaders in the field. As a young investigator, you will learn a lot just from access to these study protocols,

since they generally incorporate current best practices in the field.

Multicenter trial involvement will also give you exposure to a variety of other clinical sites and patient populations. This is helpful in understanding the variations in practice between sites. Over time, it also helps you extrapolate why results from a particular study might be more or less applicable to your own patient population based on how comparable your patients are to the study cohort.

In the DRCR.net, you have the opportunity to discuss our studies in depth with the whole group on monthly investigator calls and in person during semiannual investigator meetings. It is exciting to participate in the often-spirited discussions at these meetings. We learn a lot from one another as we discuss how to design studies that best answer our key clinical questions. The Network is open to participation and feedback from investigators, so it is easy to get involved in nearly any aspect of our protocols, from development to writing manuscripts, especially if you can recruit successfully for the studies.

Chirag Jhaveri: It is a benefit to be able to include patients across many sites to help power larger trials, and to answer questions that may be difficult to investigate individually at academic centers. There can be challenges, however, in creating a protocol that can address the unique differences between regions and practices.

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As retina specialists, although we look to evidence-based medicine, we may have our own specific practice patterns. When participating in a protocol, we have to feel comfortable following the protocol guidelines. Navigating those differences can be challenging for some, but every investigator is asked to participate only in protocols that seem scientifically sound and reasonable to them.

Dr. Punjabi: There are many benefits of participating in a multicenter trial:

- Multicenter clinical trials help us young investigators build our practices faster and get busier quicker. It is useful for referring eye doctors and primary care physicians to know we are involved in clinical trials; this can accelerate referrals and build trust and respect in the medical community.
- A number of multicenter research studies are well funded, which helps boost revenues in an age of declining insurance reimbursements. Also, the DRCR.net receives most of its funding from the NEI, so there is little to no bias involved in research methodology and results. The Network is highly respected in the retina community.
- Our patients get access to many investigational drugs and devices, sometimes even prior to FDA approval. We have excellent drugs available for many retinal diseases, but there are still many conditions with no commercially available treatment. By being involved in investigational drug studies, we can witness their results firsthand in our own patients.
- It is prestigious for us as young physicians to have our names in research publications, which can quickly accelerate our academic and research careers. Often, these studies get published in distinguished journals with a high impact factor.

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> —Omar S. Punjabi, MD

Participating in a multicenter research study also has a few drawbacks:

- Research patients need extra time and additional documentation. It takes a fair amount of work and effort to counsel patients considering a clinical trial. They usually have many questions, which can slow you down during a busy retina clinic.
- Additional visits are needed for research patients, and often it is frustrating for patients and investigators when they screen-fail for a clinical trial. Many of these patients are older and need their family members to take time off work to bring them into the office. It can be disappointing when they are not accepted into a trial.
- Conference calls and research meetings can last for a few days and take time away from our busy clinical and surgical schedules. This can be difficult when we are trying to build a practice.

Dr. Wykoff: Being intimately involved with research requires significant time and resources.

If you're not passionate about research, don't do it. Across a career, there are too many directions to pursue to spend time doing something for which you are not passionate.

I have experienced firsthand the obvious point that data integrity is critical. As an investigator, you have substantial control of how data is collected and analyzed, but much of the actual data collection itself is performed by team members such as research coordinators and certified photographers. These personnel are essential to the success of a prospective research endeavor; they need to know that the data they collect is important and that it is crucial that every piece be as accurate as possible. Protocols must be followed closely and accuracy must trump efficiency.

What advice would you offer other young retina specialists interested in incorporating research in their career?

Dr. Sun: Getting involved in the DRCR.net is a terrific way to get exposed to high-quality clinical research as a young investigator, whether you are based at an academic or private practice. My advice is to focus not only on participating by recruiting well, but also by making sure the quality of study participation in your group is excellent. I'd also advise you to find key mentors in the field early and to actively seek out opportunities for collaboration and participation in projects that interest you.

Be proactive in approaching more-experienced colleagues for advice and support; they can often give you a broader perspective invaluable in helping you to focus your efforts where they might be most fruitful. Experienced advisors can also help you design your own studies carefully so the final outcomes are informative, whether or not the results are positive.

Finally, realize that most successful research careers are built slowly over time, with patience and persistence. Don't be discouraged by early setbacks—especially in clinical research, where studies can take a lot of resources to get off the ground, be slow to recruit, and then generate data that is complicated to interpret. Enjoy the research for the sake of learning something new with each study. And remember, the studies in which you participate may lead to sweeping changes in standards of care for patients across the world.

Dr. Jhaveri: A physician has to have the enthusiasm and work ethic to become involved in clinical research. Having an excellent coordinator is the next important criterion. This may come from external hiring or finding a motivated employee who has great attention to detail. I recommend joining the DRCR.net—it is a great resource and can help guide a motivated team through all the regulatory, logistical, and practical aspects of participating in clinical trials. Active involvement will then solidify the knowledge and analytical criteria for maintaining a research center to participate in additional trials.

Dr. Punjabi: A number of retina fellowships, both academic and private, are heavily involved in research and include fellows on their research teams. Once you finish fellowship, you do not have to be part of an academic center to be involved in clinical trials. If you are a young retina physician with a keen interest and a strong motivation, it is not difficult to incorporate research into your practice.

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>
> —Chirag Jhaveri, MD

Ideas and advice for young investigators:

- Being a principal investigator (PI) for a clinical trial is lucrative. Try to get involved as a sub-investigator and be active in recruitment. Over time, we young physicians will be given more responsibility and eventually will be trusted as a PI. Many times, we may be asked to be a PI within the first few years of practice, and it is important to take advantage of the opportunities presented to us.
- Attend investigator meetings and get to know your retina colleagues. A lot of gatherings are conveniently held at the annual meetings of ASRS, the American Academy of Ophthalmology (AAO), and the Association for Research in Vision and Ophthalmology (ARVO).
- Attend investigator conference calls and be active—have your voice heard and your ideas expressed.
- Be active in recruiting patients in clinical trials.
- In each clinic lane, have a handy summary of clinical trials in which your site is involved (key inclusion and exclusion criteria, protocol schedules, etc). This allows you to quickly determine whether a patient is eligible for clinical trials.
- Be supportive and respectful of your research coordinators—they work hard and have a stressful job. They also do a lot of the behind-the-scenes work that can go unappreciated.
- Have frequent meetings and communicate with your research team regularly.

Dr. Wykoff: If you desire to be involved, don't let the abundance of data already available dissuade you into thinking there's no way to contribute. There are a multitude of opportunities that span everything from basic science to clinical applications to data interpretation to device design. Try to think beyond what is routine, look from a new perspective, and be innovative.

If you have no experience with research, start small and read the journals. Let your clinical experiences and patients stimulate research questions. Present an interesting case or case series at local or regional meetings and consider publishing the work. Know your local IRB regulations and make sure you follow them when compiling patient information for analysis.

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>
> —Charles C. Wykoff, MD, PhD

We have many excellent peer-reviewed and non-peer-reviewed journals. It's easy to feel overwhelmed by the amount of literature available—don't be. Jump in and read what you find interesting. Browse the abstracts of our major

How to Get Involved in the DRCR.net

All retina specialists are welcome to apply.

- Visit www.DRCR.net
- E-mail drcrnet@jaeb.org

Your request will be reviewed and, if approved, the necessary paperwork will be sent to you.

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journals. I skim emails from the top journals when a new issue is released to identify papers to read.

To evolve to the next level, join or start a collaborative effort. The retina research community is small and full of exceptionally insightful and hard-working colleagues. Get your friends together and brainstorm about interesting topics and questions to pursue.

I see 3 broad avenues for physicians to readily pursue prospective clinical research:

- Collaborative non-industry-sponsored trials
- Industry-initiated trials
- Investigator-initiated trials

The DRCR.net is an inspiring organization. It has successfully created a unique, enduring collaboration of academically oriented practitioners across North America committed to advancing the care of diabetic patients.

One of the most exciting aspects of the DRCR.net is its flexibility. We are always in need of sites and individuals interested in working toward the common goal of improving patient outcomes. The DRCR.net is an excellent avenue for retina physicians of any age interested in getting more involved with research. The Network is genuinely interested in new ideas and is an excellent forum to learn the intricacies of clinical trials from start to finish.

Collaboration with industry is essential to the process of bringing new pharmaceuticals and devices to market for patients' benefit. I have found interaction with the science side of industry incredibly insightful and productive. On a related note, many pharmaceutical and device companies are interested in ideas about how their products could be used in innovative ways, and are often willing to sponsor investigator-initiated trials addressing an unmet need.

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> —Charles C. Wykoff, MD, PhD

What recent DRCR.net studies you feel have made a large impact, and how are you using that information in your practice?

Dr. Sun: Protocol T, the DRCR.net comparative-effectiveness study of aflibercept, bevacizumab, and ranibizumab for eyes with DME, made a huge impact on the practice of many retina specialists by identifying that aflibercept leads to the best outcomes in eyes with worse starting vision through 1 year, although all 3 agents are similarly effective in eyes with good baseline vision and DME.

The study certainly influenced me to increase my use of aflibercept as a first-line agent in patients with vision of 20/50 or worse who are beginning anti-VEGF treatment for DME. It was reassuring, however, to see that the majority of eyes, even in the bevacizumab group, did extremely well throughout the study. Thus, I am very comfortable using the other agents for patients with DME who do not have access to aflibercept or who have previously been successful with bevacizumab or ranibizumab.

I think the results of Protocol S will also continue to inform and change the landscape of care for patients with proliferative diabetic retinopathy (PDR) as we further investigate long-term outcomes of anti-VEGF vs panretinal photocoagulation (PRP) in eyes with PDR.

Dr. Jhaveri: Both Protocol T and Protocol S have greatly influenced my practice. After explaining the results of Protocol S, I often initiate therapy with anti-VEGF instead of PRP for PDR with patients who are amenable to the treatment regimen. Protocol T influences the anti-VEGF I start with, depending on a patient's baseline vision.

I am also looking forward to learning the results of Protocol V and Protocol U, which are looking at 2 ends of the spectrum of DME—patients with very good vision and patients who have persistent edema despite anti-VEGF therapy, respectively.

Dr. Punjabi: I really like that that DRCR.net tries to formulate important questions and that it answers them in a scientific and unbiased manner. All the studies have meaningful results, but I feel the Protocol I and Protocol T data has given us some key information on how to better treat DME.

Visual acuity outcomes are always the priority, but in the real world, we have to be mindful of drug costs and patient compliance. I feel that having data from excellently structured clinical trials allows us to counsel patients better and come up with a customized plan for each patient.

Dr. Wykoff: Many of the trials having a relevant impact on clinical care delivery over the last decade have been performed by the DRCR.net. Protocol I, Protocol T, and Protocol S are great examples. Protocol T is, and will likely remain, the only well-powered, prospective trial comparing the 3 anti-VEGF agents.

Other trials in progress that I believe may have a substantial impact on guiding clinical care include Protocol V and Protocol AA. Protocol V may be particularly relevant, as it evaluates patients who previously have been excluded from our large anti-VEGF trials—those with visual acuity of 20/25 or better—and directly compares focal laser vs aflibercept vs observation.

> 'Protocol T ... made a huge impact on the practice of many retina specialists ...'
>
> —Jennifer K. Sun, MD, MPH

Leading the way

Participating in clinical trials may not be as difficult as you expect, as long as you have the motivation and initial resources. Joining the DRCR.net is a great way to get started early on in your career. The above physicians have demonstrated this and now are better doctors to their patients and are leaders in our field, shaping the way we treat our own patients as retina physicians.

Financial Disclosures

Dr. Hau – None.

Dr. Jampol – QUINTILES/JANSSEN PHARMACEUTICALS: Other, Honoraria.

Dr. Jhaveri – ALCON LABORATORIES, INC: Investigator, Other Financial Benefit; DRCR.net: Investigator, Equipment (Department or Practice), Other Financial Benefit; GENENTECH, INC: Investigator, Other Financial Benefit; REGENERON PHARMACEUTICALS, INC: Investigator, Other Financial Benefit.

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