Accelerated Cure Project for MS

September 2017

Accelerating research towards a cure for multiple sclerosis

Dear Friends,

We, at the Accelerated Cure Project, are grateful for the support that we've received from many stakeholders over the years. Since our inception in 2001, you have championed our mission and encouraged us along the way. This has allowed us to make significant progress toward our goal.

Our first article reviews the history of the Accelerated Cure Project. It includes a chronology of milestones and highlights accomplishments, facilitated by many proponents. In the second article, Dr. Farren Briggs discusses the relationship between MS and the microbiome.

This month's newsletter also features an article on the history of clinical research, which reviews the great strides that federal agencies have made in the regulation of clinical research to overcome unethical tragedies in the past.

Our partner spotlight this month is the Center for Information & Study on Clinical Research Participation (CISCRP). Their programs raise awareness about the positive impact that clinical research has on all of our lives, as well as the level of public appreciation for the dedication of clinical research volunteers.

We appreciate your support and hope that you are enjoying these first days of autumn.

The Accelerated Cure Project Team

The Accelerated Cure Project - Progress Toward a Cure

The Accelerated Cure Project's founder, newly diagnosed with multiple sclerosis, had a vision and a plan to find a cure for the disease that he struggled with. He met with MS researchers from academia and the pharmaceutical industry to learn about MS and current research and was disappointed with the lack of success. He decided that a different approach was necessary and founded a non-profit organization, now known as the **Accelerated Cure Project**, whose mission was to accelerate progress toward determining the causes of MS and ultimately finding a cure. Since its inception in 2001, the Accelerated Cure Project's mission has expanded to also include improving diagnoses and optimizing treatment outcomes for people with MS. We are grateful for the generosity and support of many donors, volunteers, partners and study participants who have enabled us to make significant progress toward that goal.

The Accelerated Cure Project's initial scientific project was to develop a Cure Map, a comprehensive and detailed plan of research focused on understanding what was known about disease origins, the state of MS research, and what gaps in knowledge existed. ACP's founder and his team reflected that the primary causes of diseases, including MS, could be grouped into five categories: abnormal genes or genetic function, infectious agents (bacteria, viruses), toxins (poisonous substances), nutrition, and trauma (physical injury or mental stress). Given the complexity of MS, it is believed that more than one of these factors in concert is likely to be the cause. Listing and investigating the possible causes of MS through development of the Cure Map helped to reveal potential promising areas of study.

From analysis of the Cure map, it became clear that research efforts toward a cure would be accelerated if there were a readily available source of biospecimens and associated clinical information for the research community at a reasonable price. This resource would enable investigators to focus their time on their research rather than sample acquisition. The ACP Repository was developed as a source of these materials. To foster collaboration within the research community and to enhance the offering, users of ACP Repository samples must agree to return their research results back to the Repository for the sharing with and future benefit of all researchers. Working with a network of 10 leading neurology clinics throughout the US, samples and data were collected from over 3,200 participants between 2004 and 2011. These samples and data were collected from people with and

without demyelinating disease. The ACP Repository continues to serve as a valuable resource for the scientific community. To date, Repository samples and data have been used in over 100 studies, more than 50 of which have returned their results to the Repository database to date, encompassing nearly 700 million data points altogether. These samples and data have enabled research studies in Multiple Sclerosis, Transverse Myelitis, Neuromyelitis Optica, and Clinically Isolated Syndrome. These studies have been conducted on a wide variety of topics, including diagnostics, genetics, immunology, risk factors and treatments/therapeutics.

To further foster collaboration in the scientific community, the Multiple Sclerosis Discovery Forum (MSDF) was launched in April, 2012. The MSDF is an interactive online venue that educates investigators who study MS and other demyelinating diseases, and provides an online venue for them to connect and share ideas. Its vision is to open paths toward new discoveries through this open communication. Currently, MSDF remains available online as a resource for researchers and others interested in learning more about MS but no new content is being developed due to a lack of available funding. With additional funding MSDF could continue to serve the scientific community as a resource for information about MS research findings, opportunities for researchers to discuss and debate the implications of new findings, resources, and much more.

The importance of understanding the MS experience from the perspective of people with MS (PwMS) is essential to improve their treatment and care. With this in mind, ACP partnered with the Complex Adaptive Systems Initiative at Arizona State University and Feinstein Kean Healthcare to create iConquerMS™, a national people-powered research network for MS. Funded by the Patient-Centered Outcomes Research Institute (PCORI), iConquerMS was launched in February 2015 as a part of a national research network called PCORnet. Governed and driven by people living with MS, iConquerMS was developed to improve health, healthcare, and quality of life for people with MS by connecting those affected by MS, clinicians, and researchers, and inspiring them to work together to accelerate innovation, research, and the application of new knowledge. To date, over 4,100 individuals have participated. The initiative's portal enables all people living with MS to play an active role in research. Participants are able to easily and privately take surveys about their daily experiences and symptoms, and share their medical records. The

portal also contains information about research in general, and participants can receive updates on recent discoveries and suggest areas of research that are of interest to them. In 2016, iConquerMS launched the REAL MS™ (Research Engagement About Life with Multiple Sclerosis) initiative, a research study that will follow participants over time. Every six months, participants in REAL MS are invited to provide updated information related to their experiences with MS including treatment status and response, symptoms, and any relapses they may have experienced. Each launch of REAL MS surveys also incorporates feedback from the community for new areas to study, including the recently launched Wellness survey focused on complimentary and alternative medicine. The collected information is pooled with similar information from thousands of others living with MS, participating in iConquerMS. Researchers can use the collected data to detect patterns that would not be visible otherwise, and use these patterns and insights to figure out the causes of MS, determine who will respond best to various treatments and find new, improved treatments. REAL MS also offers researchers the opportunity to conduct special data collection activities via iConquerMS; to collect biosamples; and to recruit individuals with certain characteristics for their studies.

In general, minority populations are severely underrepresented in scientific research (read more in the article Clinical Research- A Journey Toward Diversity). This makes it difficult to understand many disease processes and what treatments are effective for people of different ethnicities. There is a tremendous need to involve minority communities in the design and development of research, and to increase their enrollment in clinical studies. For example, recent studies show that African Americans may have the highest risk not only for MS, but for more aggressive forms of the disease. Additional studies are needed to better understand why this population is at greater risk. In October 2016 ACP led an effort to develop the Multiple Sclerosis Minority Research Engagement Partnership Network. In this survey-based initiative, information is being collected to better understand how people with MS from different ethnic backgrounds and races view medical research, with the goal of developing solutions that will increase minority enrollment in MS research studies, including iConquerMS.

ACP has partnered with a number of organizations over the years in its quest to improve diagnoses, treatment outcomes, and ultimately develop a cure for MS. ACP has received tremendous support from donors and volunteers who are inspired by our mission and approach. Leading neurology clinics have worked with ACP to recruit thousands of

research participants from their patient populations. These research participants and their families have generously given their time to make the clinical studies sponsored by ACP a success. We, at the Accelerated Cure Project, are grateful for all of our supporters. You have enabled us to make significant progress in our mission. We look forward to the future as we continue to work together to promote scientific collaboration and enable researchers worldwide to make more breakthroughs in MS research at a faster pace.

The Microbiome and MS

By Farren Briggs PhD, ScM

Human… What is a *human*? We think of the human being as a singular organism, but in fact a human being is an ecosystem – which we call the human microbiome. This ecosystem is the collective combination of human cells, microbial cells (microbiota), and the genes within these cells,that exist on and in a human being. Actually, the human microbiome is more *other* than it is *human* – only a third (if that) of the cells and <1% of the genes we carry around in this human ecosystem are human (**Figure 1**). Don't be grossed out though, most of these bacterial and fungal cells are really important to our existence – as a human, we live in a symbiotic relationship with these *other* cells. We provide shelter, resources, and food through what we eat, and they in turn provide protection and help break down certain foods, aiding our digestion. The microbial cells exist on all our surfaces, but they are predominantly within our gut – hence you may have heard the term gut microbiota. NPR created this neat must-watch animation describing the human microbiome and the important role these *other* cells play in our lives (click here to see the video). Unfortunately, we have barely scratched the surface of understanding how changes in the human ecosystem impact our health and vice versa.

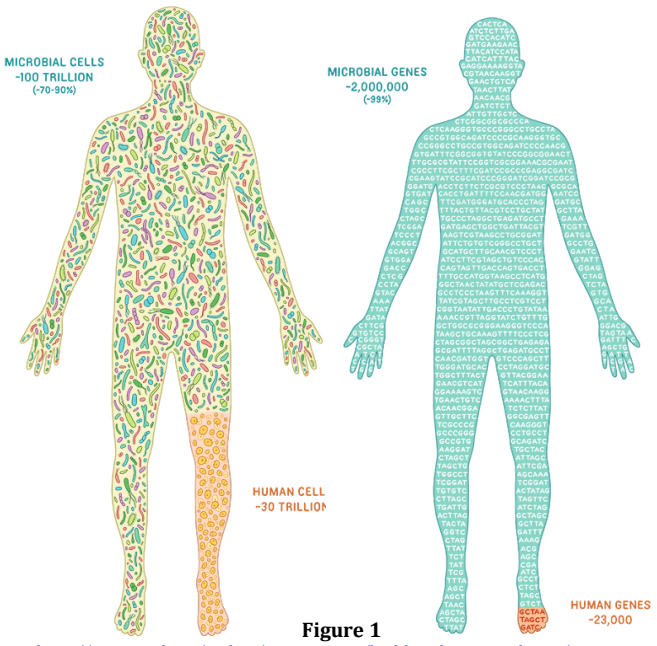
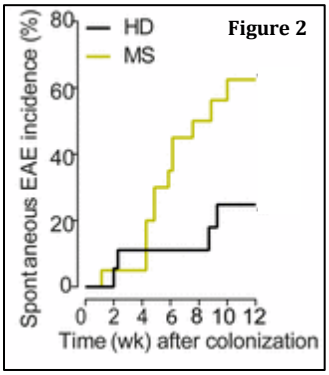


Figure 1

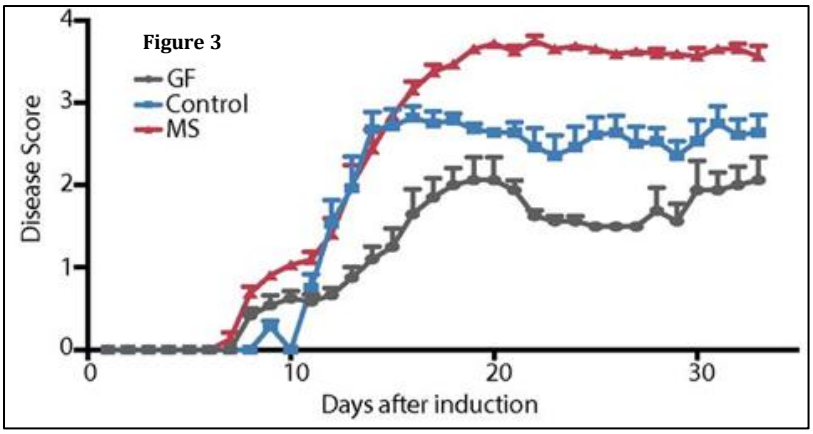
https://www.amnh.org/explore/science-topics/health-and-our-microbiome/meet-your-

This month, two papers were published simultaneously in the official journal of the National Academy of Science (*PNAS*) shedding light on the possible role the microbiome may have in MS. In both *PNAS* papers the gut microbiota (from fecal samples) was compared between persons with MS (PwMS) to those without MS, and then the researchers assessed the impact of the human microbiota on mice susceptible for neurological autoimmunity. The results were surprisingly and intriguingly similar. The first study out of Germany, compared the gut microbiota of 34 identical twins pairs.[1] In each twin pair only one sibling had MS (thus, the twins were discordant for MS). The microbiota between the twins with and without MS did not differ dramatically. However, half of the MS twins were on disease-modifying therapies. When the analysis was restricted to drug-naïve MS twin pairs, there was an elevated abundance of *Akkermansia muciniphila* in the fecal sample from the MS twins compared to their healthy co-twins. The researchers then transplanted the human microbiota into unique mice that could spontaneously develop a MS-like phenotype. As one would expect, only a handful of the human-derived microbiota were able to colonize the gut of these mice. Well, the mice who received the microbiota of the MS twin were more likely to spontaneously develop the MS-like condition than the mice who received the microbiota from the healthy twin (HD) (**Figure 2**). These mice with the MS microbiota produced less immune cells secreting IL-10 (an anti-inflammatory molecule), than the mice with the HD microbiota.



[1] https://www.ncbi.nlm.nih.gov/pubmed/28893994 (or http://www.pnas.org/content/early/2017/09/05/1711233114.full)

The second *PNAS* paper describes an American study where the gut microbiota of 71 drug naïve PwMS were compared to 71 unaffected controls. [2] There were no major differences in the microbiota composition, but they did observe *Akkermansia muciniphila* and *Acinetobacter calcoaceticus* as being increased in PwMS (similar to the German study). The researchers took gut bacteria and immune cells from each individual and mixed them. The MS immune cells stimulated with the MS gut bacteria were not fully functional (they were impaired) – this demonstrated the microbiota may influence the immune system in PwMS. Then mice prone to another MS-like condition were colonized with the microbiota from PwMS and unaffected controls. In these mice, they will all develop the MS-like condition. What was interesting, was the severity (disease score) of the MS-like condition was worse in mice who received the PwMS microbiota, compared to those from the unaffected controls, and much worse than the mice who stayed germ-free (GF) (**Figure 3**). And similar to the prior study, the mice with the MS microbiota produce few immune cells secreting the anti-inflammatory molecule IL-10.



It is rare to have two studies complement each other so well, particularly with such unique study designs and results. Nonetheless, these results should be cautiously interpreted, as there is so much yet to uncover. However, they do suggest a strong role for the gut microbiota in MS (in mice, so far), both at onset and on severity. Many things influence microbiota hitching a ride in/on our bodies, particularly diet (there is robust work demonstrating switching between animal- and plant-based diets rapidly and reproducibly alters the gut microbiota).[3] All in all, these results are exciting, and I am sure we will see many more diet-related studies in MS, with specific considerations for our hitchhikers, in the next few years!

---

[2] https://www.ncbi.nlm.nih.gov/pubmed/28893978 (or http://www.pnas.org/content/early/2017/09/05/1711235114.full)

[3] http://www.nature.com/nature/journal/v505/n7484/full/nature12820.html

Clinical Research – A Journey Toward Diversity

Clinical trials are an essential part of the drug development process. Regulatory agencies such the Food and Drug Administration (FDA) use information gathered from clinical trials to decide if medicines are safe and effective. It is important to have ethnic diversity in clinical trials to better understand diseases, and the full impact of certain drugs. Different ethnicities can have unique responses to the same disease. Studies have shown that MS can be especially active in African Americans. The effectiveness of many drugs can also vary depending on the patient's ethnicity, lifestyle, culture and genetic makeup. For example, about 50 percent of Asian patients and 75 percent of Pacific Islanders lack the enzymes required to activate Plavix (a blood thinner). Certain classes of hypertension drugs have recently been found to be less effective in African American patients.

According to the National Institutes of Health (NIH), minorities account for fewer than 10 percent of patients enrolled in clinical trials. African American men are twice as likely as Caucasian men to die from prostate cancer, yet they represent just 4 percent of prostate cancer clinical trial participants. Suicide is one of the top three causes of death among Asian American women under 45 years of age, yet they represent just 1 percent of major depressive disorder clinical trial participants. And while the prevalence of diabetes among Mexican Americans and Puerto Ricans is more than double that of Caucasians, those groups combined represent just 4 percent of diabetes trial participants. Many research findings cannot be applied to minorities because they are not represented in the clinical trial data that has been collected.

One primary reason for low participation rates in clinical trials among minorities is a lack of trust among potential participants. This mistrust is based on a long history of unethical clinical research. This, and a general lack of trust in health care institutions or the health care system in general, have negatively affected the participation of minorities in research.

The Tuskegee Syphilis Study is probably the worst case of unethical human subjects research in the history of the United States. This was a research project conducted by the U.S. Public Health Service. Six hundred low-income African-American men, 400 of whom were infected with syphilis, were monitored for 40 years. Free medical examinations were given; however, subjects were not told about their disease. Researchers withheld treatment even when penicillin became widely available. Researchers did not tell the subjects that they were in an experiment. Many died of the disease, infected their wives, and/or passed congenital syphilis to their children. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare. President Clinton apologized to study subjects and their families in 1997, however residual mistrust of clinical trials remains today among many members of the African-American community.

German physicians conducted medical experiments on thousands of concentration camp prisoners without their consent during World War II. Most of the subjects in these experiments died or were permanently crippled as a result. After the war, some of those responsible for these atrocities were brought to trial. These trials; held in Nuremburg, Germany, led to the formulation of the Nuremberg Code in 1948. The Nuremburg Code was the first international document stating that subjects should give consent for participating in research and that the benefits of research must outweigh the risks.

In the late 1950s, thalidomide was approved as a sedative in Europe. It was *not, however,* approved by the Food & Drug Administration (FDA) in the United States. Thalidomide was prescribed to control sleep and nausea throughout pregnancy, but it was soon found that taking this drug during pregnancy caused severe deformities in the fetus. Many patients did not know they were taking a drug that was not approved for use by the FDA, nor did they give informed consent. Some 12,000 babies were born with severe deformities due to thalidomide. This disaster led to the adoption of the Kefauver Amendments to the Food Drug and Cosmetic Act, requiring drug manufacturers to prove to the FDA the effectiveness of their products before marketing them.

In the 1960's, hepatitis experiments were carried out on mentally disabled children at the Willowbrook State School in Staten Island, N.Y. These experiments were approved by the New York Department of Health. Researchers intentionally infected subjects with hepatitis and observed its natural progression. The investigators maintained that hepatitis infection was inevitable for this population. However, only children whose parents gave permission to participate in the studies were admitted to Willowbrook. The consent process for this study was unethical in light of this coercive admission policy.

Henrietta Lacks was a poor, African-American mother of five who died in 1951 of cervical cancer. Before Lacks died, a research team at Johns Hopkins University in Baltimore took a sample of tissue from her cervix. Researchers found that they were able to grow these cells in dishes, which fueled a cell line called HeLa cells. This was a major breakthrough that gave researchers a powerful new tool against disease that has since generated billions of dollars. The first benefits from HeLa cells were in their use in developing the first vaccine against polio. More than 60,000 articles have been published based on the use of HeLa cells, including cancer and AIDS research. There has been much controversy over the fact that Lacks never agreed that these cells could be used for research. For years, her own family had no idea that her cells were still alive in petri dishes in scientists' labs. Scientists collected the family's blood to map HeLa genes without proper informed consent after they learned of the cell line's existence. Despite this, the Lacks family remains supportive of research that has been done and recently endorsed restricted access to HeLa genome data. Under an agreement with the National Institutes of Health, Lack's genome data is accessible only to those who apply for and are granted permission. Two representatives of the Lacks family now serve on the NIH group responsible for reviewing biomedical researchers' applications for controlled access to HeLa cells. Additionally, any researcher who uses that data is asked to include an acknowledgement to the Lacks family in their publications.

The Declaration of Helsinki was developed by the World Medical Association in 1964. This is a set of ethical principles for clinical research that is the basis for Good Clinical Practices used today. The Declaration of Helsinki states that informed consent from research participants is necessary, and that the risks of research should not exceed its benefits. According to this Declaration, research should be conducted by medically and scientifically qualified individuals, and be based on the results from laboratory and animal experimentation. Finally, the Declaration of Helsinki states that research protocols should

be reviewed by an independent committee prior to initiation. As a result, all research involving human subjects in the U.S. must be reviewed and approved by an ethics committee, or an Institutional Review Board (IRB).

The National Research Act was approved by Congress in 1974, creating the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct of clinical research involving human subjects and to develop guidelines to be followed when conducting such research. The Commission drafted the Belmont Report, which established three basic ethical principals in clinical research: respect for persons, beneficence, and justice. Respect for persons dictates that individuals participating in research must be given the opportunity to choose what happens to them and those that are less capable are entitled to protection. This is the foundation for the informed consent process that is currently used in clinical research. The consent form must include sufficient information for potential subjects to understand the procedures, benefits and risks of a given study, and to make a voluntary choice to participate. Beneficence is the principal that clinical research should maximize possible benefits and minimize possible harms so that human subjects are not harmed. Justice requires that the selection of research subjects be done in a manner that distributes the benefits and risks of research fairly. These three ethical principals are the cornerstones for regulations involving human subjects today.

The Common Rule was adopted in 1991 as the federal policy regarding human subject protection. The Common Rule is the baseline standard of ethics to which any government funded research in the United States is held. Nearly all academic institutions in the US hold their researchers to these statements of rights, regardless of funding. The Common Rule includes requirements for researchers obtaining and documenting informed consent; and requirements for IRB membership, review of research and record keeping. The Common Rule also includes additional protections for certain vulnerable research subjects (pregnant women, prisoners and children), and requirements for assuring compliance by research institutions.

The current regulations, which have been in place since 1991, were developed at a time when research was conducted predominantly at universities and medical institutions, and each study generally took place at a single site. Since then, research with human participants has grown in scale and become more diverse and data has become digital. In 2017, the U.S. Department of Health and Human Services (DHHS) and 15 other federal agencies issued a Final Rule to update the regulations, which allows more flexibility in keeping with today's dynamic research environment. The new rule strengthens protections for people who volunteer to participate in research. For example, it includes a requirement for consent forms to provide potential research subjects with a better understanding of a project's scope (including its risks and benefits), so they can make a more fully informed decision about whether to participate. The Final Rule also includes a requirement that consent forms for some federally funded clinical trials be posted on a public website. The Final Rule also ensures that the oversight system does not add inappropriate administrative burdens, particularly to low risk research. For example, it includes requirements to use a single IRB for multi-institutional research studies, eliminates continuing review for some minimal risk research, and establishes new exempt categories of research based on the level of risk they pose to participants. In addition, the Final Rule includes behavioral health studies in the definition of clinical trials. Researchers using stored identifiable data or biospecimens for their studies will have the option of relying on broad consent obtained for future research. Pending review of the current administration, the effective date for all changes except cooperative research (projects involving more than one institution) is January 2018. Changes to cooperative research requirements will be effective in January 2020.

The Code of Federal Regulations includes rules for the protection of human subjects in studies involving any test article subject to FDA regulation (i.e. drugs, devices, food/color additives). 21 CFR Part 50 includes regulations for informed consent, and additional safeguards for children in these studies. 21 CFR Part 56 includes regulations regarding Institutional Review Boards. In addition, the NIH and Office for Human Rights Protection (OHRP) have required all people conducting or overseeing human subjects research to have training in research ethics since 1999.

The federal regulation of clinical research has made great strides from a dark past to protect the rights of those that volunteer to participate in clinical research. Additional work must continue that couples these assurances with effective recruitment methods to ensure that

minority and vulnerable populations are reached and engaged in meaningful and respectful ways. Improving diversity in clinical trials is essential to providing medical products that are safe and effective for everyone.

In October 2016 the Accelerated Cure Project was approved for a Eugene Washington PCORI Engagement Award by the Patient-Centered Outcomes Research Institute to support the development of the Multiple Sclerosis (MS) Minority Research Engagement Partnership Network. This network, developed in partnership with Feinstein Kean Healthcare, is designed to identify disparities and increase participation by minorities in MS medical research.

Partner Spotlight - CISCRP

Medical advances made possible by clinical research regularly touch every person's life. More than half of all Americans are currently taking prescription medications and most Americans routinely use over-the-counter medications. Behind every treatment there are thousands of people that volunteered to participate in clinical trials. People don't usually connect medical advances, including these medicines, to clinical research and the dedication of research volunteers who made these developments possible. Clinical research is usually only discussed in a doctor's office when a patient is diagnosed with an illness. In addition, media coverage tends to focus on the negative occurrences in medicine, such as conflicts of interest among medical professionals or tragic errors resulting in harm to patients. This has created poor public perception of clinical research, and eroded the public's trust in its ethics and safety. The Center for Information & Study on Clinical Research Participation (CISCRP) is a Boston-based non-profit organization, founded in 2003, dedicated to changing this by raising awareness about the positive impact clinical research has on all of our lives and raising the level of public appreciation for the dedication of clinical research volunteers.

CISCRP offers a variety of resources, programs and services that provide a better understanding about clinical research and the role each party plays in the process. Doctors are often perceived as the heroes in medicine. While there are many outstanding physicians who provide excellent care to their patients, the fact that medical breakthroughs wouldn't

be possible without the generosity of clinical trial volunteers is often overlooked. The Medical Heroes program recognizes clinical trial volunteers, or "Medical Heroes", for their gift of participation and increases awareness about clinical trial participation. Medical heroes are ordinary people who have chosen to give the gift of participation in clinical research despite possible risks. This gift profoundly contributes to the knowledge about the nature of disease, its progression and how to treat it; and ultimately benefits future generations.

Studies show that most clinical trial participants want to know the results of their trial, however almost none are given this information. Providing trial results can improve the transparency of clinical research, and help close the loop with patients. CISCRP's Communicating Trial Results program provides study volunteers with clinical trial results by creating and delivering summaries in everyday language. Volunteers in the medical community serve on an editorial panel that reviews these summaries to be sure that they are easy to understand, unbiased and accurate. With the help of this editorial panel, CISCRP "translates" the technical results of clinical trials into lay summaries. This provides ongoing communication with participants and keeps them informed about their study's results after it ends.

Finding a clinical trial can be confusing for many patients. Search Clinical Trials is a free service that CISCRP offers to help people find relevant clinical trials. CISCRP staff will search clinical trial listings and send the contact information for research studies to interested participants. They also offer free educational brochures that contain important information to consider about participating in clinical research and key questions to ask research staff before enrolling in a clinical trial. Patients providing an email address as a part of their clinical trial search can also receive a quarterly newsletter to help stay informed about CISCRP's programs, and clinical research in general.

CISCRP has an extensive library of educational resources intended to help the general public learn about clinical research and what it means to volunteer for a study. Their brochures provide basic information about clinical research, including patient protections, and resources for potential research volunteers. Their educational videos, offered in a variety of languages, describe the clinical research process through real-life experiences of clinical research participants. CISCRP's library of resources also includes The Gift of Participation: A Guide to Making Informed Decisions About Volunteering for a Clinical Trial, which is a complete resource for study participants. Written by the founder and

chairman of CISCRP, it covers why participation in clinical research really matters, addresses what participation means and how it helps to advance medical science. This book also contains practical information on insurance coverage, compensation, and tax ramifications for clinical research volunteers. CISCRP also hosts the online community, HealthUnlocked – Understanding Clinical Trials, that is dedicated to educating the public about and engaging them in clinical research.

CISCRP holds special events nationwide throughout the year. AWARE for All is a free program whose goal is to educate the public in making informed decisions about clinical research participation. AWARE events typically include free health screenings, informational exhibits, local physician and patient speakers, and a reception to honor clinical research participants. CISCRP sponsors 5K run & walk events throughout the year to celebrate the people who volunteer for clinical research. CISCRP also hosts informative webinars on a variety of topics for both professionals and the public that share research findings, program updates, and educational presentations.

CISCRP does not recruit for clinical trials, rather they work to inform the public about clinical trials and why they might, or might not want to participate. Their programs recognize all of the men and women who participate in clinical research. Their participation not only advances our current knowledge about disease, but it improves medical knowledge for generations to come.