# RESEARCH *Matters*

WINTER 2019

## IN THIS ISSUE...



Association for the Accreditation of Human Research Protection Programs, Inc. — *Full* Accreditation

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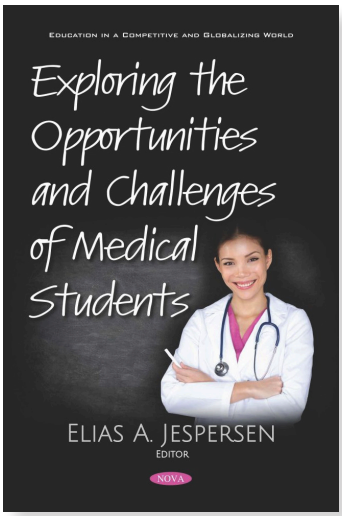
# RESEARCH AROUND McLAREN

## McLAREN FACULTY BECOME AUTHORS




"We are excited to share that McLaren Macomb faculty and trainees recently published two chapters in the book *Exploring the Opportunities and Challenges of Medical Students* published by NOVA Science Publishers, Inc (New York)," says Pam Royston, PhD, Director of Medical Education.

To training hospitals like McLaren, these chapters provide a glimpse of the level of Quality Improvement (QI) and research training medical students obtain prior to residency. The Accreditation Council for Graduate Medical Education, the accrediting body for residency, puts emphasis on these competencies by requiring residents to participate in research and QI activities and annualy tracks outcomes such as peer-reviewed publications and presentations.

The first chapter was authored by Anila Rao, DO (IM Resident), Elizabeth Brooks, DO, (IM Faculty), Ashley Harnden, DO (GS Faculty), Lori Mills, MLIS (Librarian), Thomas Alderson, DO (OB Gyn Program Director), Jim McQuiston, DO (GS Program Director), and Grace Brannan, PhD (Research Advisor). This chapter is a systematic review of medical students' QI education. This chapter showed continuous growth in medical students' QI knowledge throughout their education. Medical students QI projects contributed to organizational change and patient benefit in a majority of the studies reviewed.

The second chapter was authored by Clarissa Dass, DO (Cardiology Fellow), Melissa Ianitelli, DO (Cardiology Faculty) and Grace Brannan, PhD (Research Advisor) along with external collaborators. This study focused on assessing the impact of two research programs on osteopathic medical students. Osteopathic students in this study were inclined to engage in research, which will likely increase their potential success in meeting residency requirements. The increase noted in both programs and the equal participation of female and male medical students were very encouraging and points to gender as a non-factor in scholarly experience for entering residents contrary to earlier trends. While students were more exposed to clinical research and with increasing responsibility throughout medical school, we found the experiences to be varied and needing further bolstering during residency.

The knowledge gained from these studies will hopefully aid residency programs in identifying competencies and needs of residency applicants and new trainees in their program. In addition, based on these findings, medical students rotating through McLaren could potentially engage in QI projects and contribute to the health and wellbeing of patients.

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For details about the study, the complete citations are:

*1. Brooks, E., Rao, A., Harnden, A., Mills, L., Alderson, T., McQuiston, J., and Brannan, G.D. Chapter 1: Quality improvement education for medical students: a systematic review. In: Jespersen, EA, ed. Exploring the Opportunities and Challenges of Medical Students. New York: NOVA Science Publishers, Inc. 2019: 1-29.*

*Dass, C., Ianitelli, M., Tolentino, D., Gerome, J., Wadsworth, N., and Brannan, G.D. Chapter 2: Experiential research and scholarly programs for medical students: short-term paradigms. In: Jespersen, EA, ed. Exploring the Opportunities and Challenges of Medical Students. New York: NOVA Science Publishers, Inc. 2019:*

# HEART FAILURE RESEARCH HOPES TO PROVIDE FURTHER CARE TO PATIENTS

McLaren is taking part in the GUIDE HF clinical trial in hopes of providing further care to patients suffering from heart failure. The study is attempting to expand the usage of the CardioMEMS HF system device.

"Currently, the CardioMEMS HF System is approved for New York Heart Class III patients who have had a heart failure admission in the past 12 months," said Dr. Kalil Masri, cardiologist at McLaren Bay Region. "The purpose of the study is to determine if this device will help reduce hospitalizations for a wider group of heart failure patients, NYHC II -IV, who may not have a hospitalization. McLaren is 1 of 140 centers that is participating in this important trial."

The CardioMEMs device is used to help patients catch heart failure in early stages. "When your heart is not able to pump effectively, fluid builds up and causes pressure increases in your pulmonary artery and lungs," said Dr. Masri. "If left untreated, it causes the heart to get weaker over time. The CardioMEMS HF system is a tiny pressure sensing device inserted into the pulmonary artery. The device measures the PA pressure and wirelessly sends it to your healthcare provider so they can identify the silent symptoms of advancing heart failure and takes steps to control it before it gets worse."

Kalil Masri, DO

The CardioMEMS HF System enables earlier and more proactive treatment and reduces the risk of rehospitalization. The CardioMEMS HF System is the only FDA-approved PA pressure monitoring system available today. Over 11,000 patients have received the CardioMEMS HF System since it became available in 2014. Prior studies have shown that when a patient's heart failure is managed using the CardioMEMS HF System, they have improved quality of life and a reduction in heart failure hospitalizations.

"With further research expanding indications for the CardioMEMS device, more of the heart failure population will benefit from earlier heart failure treatments, thus reducing cardiac decompensation and heart failure hospitalizations," said Dr. Masri.

The CardioMEMS HF System supports heart failure management by measuring pulmonary artery pressure from within the body. Building on previous clinical trials, the GUIDE HF trial will study whether the CardioMEMS device can improve survival and quality of life for those living with heart failure.

"Heart failure is a very complex disease and there has been very little advance in the treatments," said Dr. Masri. "While current treatments have been successful in treating some heart failure patients, there are a large number that still lack sufficient therapies. Research matters because it provides investigation of new, effective, and safe treatments that will improve the quality of our patients."

## ARE YOU INTERESTED IN BECOMING A RESEARCH PARTICIPANT?

**For information on enrolling in a clinical trial please visit our website at https://www.mclaren.org/main/research-trials1.aspx . Here you will find a list of open enrolling studies at McLaren, including which hospital the research is being done at and contact information for each study.**

**We have enrolling studies for the following conditions (not a complete list):**

- **Diabetes**
- **High Blood Pressure (Hypertension)**
- **Stroke**
- **Heart Attacks / Heart Failure / Heart Disease**
- **Kidney Diseases**
- **Lung Diseases**
- **Peripheral Artery Disease**
- **Carotid Artery Disease**
- **Mastectomy**
- **Various Cancers**
  - **Breast**
  - **Lung**
  - **Prostate**
  - **Multiple Myeloma**
- **Patients who underwent intracranial aneurysm coiling**
- **Drug study for patients with recent acute coronary syndrome**

**For a complete list of conditions, please visit our website listed above.**

# RESEARCH AROUND McLAREN


*Some of the McLaren ACC attendees posing near the McLaren display table. From left to right: Andrew Jablonski, Macomb Cardiology NP; Chandan Gupte, VP of Clinical Excellence and Research; Dr. Timothy Logan, Macomb Attending Cardiologist; Dr. Clarissa Dass, Macomb Cardiology Fellow; Dr. Adam Bykowski, Macomb Cardiology Fellow; Nicole Prentice-Gayton, Macomb Cardiology Fellow; Rebecca Ayers, Macomb Clinical Manager of Cardiology; Dr. Vivek Sengupta, Macomb Chief Cardiology Fellow; Dr. Mark Zainea, Macomb Attending Cardiologist; and Pam Wills-Mertz, Director of the McLaren Center for Research and Innovation.*

## MCRI GOES TO THE AMERICAN COLLEGE OF CARDIOLOGY (ACC) CONFERENCE

The McLaren Center for Research and Innovation was proud to be a hospital partner level sponsor for the 31st Annual Michigan Chapter ACC (American College of Cardiology) Conference on November 8 and 9, 2019.

The conference is an annual meeting of cardiologists, fellows-in-training, nurses, nurse practitioners, physician assistants, industry sponsors and other cardiac care providers. The meeting this year was held in Grand Rapids. McLaren's own cardiologist, Dr. Timothy Logan is on the conference planning committee. This conference was an excellent event to network outside of McLaren, as well as educate on research programs at McLaren. Many McLaren fellows were present to share their vast cardiology knowledge, as well as scholarly activity projects.

Among the many events of the conference, the fellows-in-training get to compete in team Jeopardy consisting of advanced cardiology care questions. The McLaren team took 2nd place in the state of Michigan! Congratulations and a job well done to team members: Dr. Vasim Lala, Dr. Victor Hunyadi, and Dr. Vivek Sengupta!

McLaren was also well-represented in case presentations and research posters:

Dr. Vasim Lala (Macomb Cardiology Fellow) gave an oral presentation titled, "A Rare Case of 'broken heart' causing papillary muscle rupture".

Dr. Hafiz Khan (Flint Cardiology Fellow) presented a poster titled, "Anomalous


**We sincerely regret if we left out any fellow or resident, but we had a publication deadline. Nevertheless, our congratulations to all of you that received any recognition for your scholarly activity work. We also like to recognize faculty, program directors, and all medical education staff for the support and assistance. Without you, none of this would have been possible.**


*Betsy Felton, McLaren Director of Cardiovascular Service Line*


*Dr. Michael McKenna, McLaren Chief Medical Officer, and Chandan Gupte, McLaren VP of Clinical Excellence and Research*


*McLaren Flint Cardiology Fellow Dr. Hafiz Khan.*

Origin of Left Main Coronary Artery from the Right Sinus of Valsalva along with Right Coronary Artery".

Dr. Victor Hunyadi (Macomb Cardiology Fellow) presented a poster titled, "A Rare Case of Aortic Valve Cusp Rupture Post Balloon Aortic Valvuloplasty Prior to Implantation of a Transcatheter Aortic Valve Replacement".

Dr. Clarissa Dass (Macomb Cardiology Fellow) presented a poster titled, "Thirty-day Readmission Rate after Percutaneous Coronary Intervention: A Retrospective Study".

Best poster award was presented to Dr. Vivek Sengupta (Macomb Chief Cardiology Fellow) for his poster titled, "Percutaneous Management of High-output Heart Failure due to Iatrogenic Aortocoronary Venous Grafting to the Coronary Sinus".

**Congratulations to all that presented! You've made McLaren proud!**

## McLAREN MACOMB RESIDENTS REPRESENTED McLAREN AT THE ANNUAL MICHIGAN OSTEOPATHIC ASSOCIATION SCIENTIFIC RESEARCH EXHIBIT COMPETITION.

*Pictured are (left to right): Internal Medicine Resident Dr. Rasanjeet Singh; Family Practice Resident Dr. George Fakhouri; Internal Medicine Resident Dr. Anila Rao; Internal Medicine Resident Dr. Alexandra Davies; and Internal Medicine Resident Dr. Akarsh Parekh. Congratulations to Dr. Anila Rao for winning an award on her presentation titled "Polycythemia Vera: An Unusual Cause of Heart Failure."*

# RESEARCH AROUND McLAREN

Vidya Yarlagadda

Tanya Gardner-Mosley

## REGULATORY SPECIALISTS... WHO, WHAT AND WHY!

McLaren Center for Research and Innovation has some very specialized team members handling essential regulatory submissions and communications for new and ongoing research. As researchers, you may not even know they're there, but in the background, these specialists are performing vital tasks under extreme deadlines to ensure MCRI's studies are opened in a timely manner and stay in regulatory compliance during the course of the study. Regulatory specialists are on the front line with the sponsors ensuring consent forms are appropriate, completing IRB applications, tracking essential documents and training for research staff, requesting investigator's signatures, all on a very tight time line. "This can be a high-pressure job", says Vidya Yarlagadda, MCRI Regulatory Specialist. "We have to move quickly and accurately to keep the entire project on track."

> "LEAVING THE SITE STAFF AND INVESTIGATORS FREE TO IDENTIFY AND ENROLL PATIENTS INTO STUDIES IS KEY. NOT HAVING TO WORRY ABOUT REGULATORY HOPEFULLY GIVES THEM THE TIME THEY NEED FOR SUCCESSFUL ENROLLMENT. THIS IS THE GOAL."
>
> **– Vidya Yarlagadda**
> **MCRI Regulatory Specialist**

Tanya Gardner-Mosley, Sr. Regulatory Specialist knows that pressure all too well. "Yes, this can be challenging! But what I really love is to see these new opportunities become available to patients at McLaren, and it's satisfying knowing that I played such a big part in their care."

Regulatory specialists routinely field questions, comments and concerns from a variety of stakeholders. The IRB, the sponsor, the site staff, investigators and administration all have a vested interest in the regulatory activity of a study. "They all want things done in very specific ways," said Tanya, "and it can be like a juggling act; with shifting priorities, timelines and expectations. There really is never a dull moment!"

MCRI Regulatory Specialists support investigators conducting research at five active research sites throughout McLaren. They service multiple service lines, including Cardiology, Vascular Surgery and Neuroscience. Most of the studies supported by the regulatory team are industry funded drug and device clinical trials. However, because McLaren is a Comprehensive Stroke Center, we are also conducting NIH funded trials through StrokeNet. "We submit studies to a variety of external IRBs, which all operate on different platforms," says Vidya. "so, there's a lot to manage! But it's exciting to always be learning something new," she adds.

"The regulations regarding research are always changing, we have to really work at staying educated and keep up with new information," says Vidya. "We try to attend educational sessions, webinars or classes offered regarding regulatory compliance so we can stay ahead of the changes." Understanding the framework that research is built on is vital to success as a regulatory specialist. The regulatory specialist is one of the first team members to get the study documents and really learn the protocol. Their ability to understand the study and the operations at the site are key to their ability to complete IRB applications and consent forms properly. "Having been a coordinator in the past makes my job much easier," explains Tanya, "some Research Institutions don't have regulatory specialists, so all this work falls on the coordinators and investigators. I'm happy MCRI can offer this service to our sites!"

"Leaving the site staff and investigators free to identify and enroll patients into studies is key. Not having to worry about regulatory hopefully gives them the time they need for successful enrollment. This is the goal," says Vidya.

To get in touch with the MCRI Regulatory staff about an ongoing project, call 248-484-4960 or email: regulatory.research@mclaren.org.


*Abhinav Deol, MD*
*(Photo by Tamara Collins)*

# CAR-T THERAPY – "SMART BOMBS" AGAINST BLOOD CANCERS

According to Abhinav Deol, MD, program director of Hematology and Oncology Fellowship at the Barbara Ann Karmanos Cancer Institute in Detroit, and associate professor in the Department of Oncology at Wayne State University School of Medicine, it's been amazing to see the rapid change in hematology oncology over the past few years. We continue to accelerate the pace of progress to bring new treatment advancements to more people.

Our team at Karmanos Cancer Institute has helped drive many of treatment advancements for blood cancers, with particular success in stem cell transplant therapy. We were the first cancer center in Michigan approved to treat adult patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL) with the commercially-approved chimeric antigen receptor (CAR) T-cell therapy. DLBCL is the most common form of adult non-Hodgkin lymphoma in the U.S., accounting for 30 percent of new cases. CAR-T is also approved for acute lymphoblastic leukemia (ALL) and we offer patients the option of exploring stem-cell transplant for several other forms of leukemia.

CAR-T therapy is at the cutting-edge of developing treatments for certain cancers. The concept itself sounds like science fiction – arming one's own immune system to fight off the cancer. We collect the patient's white blood cells using an apheresis machine. Once collected, these cells are sent to the manufacturing facility where they are genetically modified using a DNA template. The cells, which are transformed to CAR-T cells, are able to recognize a specific marker expressed on the surface of the cancer cell. The manufacturing process takes a few weeks. After a mild round of chemotherapy, the CAR-T cells are infused back into the patient.

These modified T-cells go to work as cancer "smart bombs" destroying the cancer cells. These cells not only destroy the cancer cells they engage with but also divide inside the patient's body to create an army of CAR-T cells to recognize and eliminate more cancer cells. Most serious side effects occur within a week to 10 days after the infusion of the armed cells. Patients are closely monitored by Karmanos' highly trained and experienced medical team who are able to recognize the unique side effects of this therapy.

According to Dr. Deol, the outcomes can be remarkable, especially for patients whose disease was not controlled, despite multiple rounds of conventional

*CONTINUED ON PAGE 16*

> "AS A NATIONAL CANCER INSTITUTE-DESIGNATED COMPREHENSIVE CANCER CENTER, OUR CLINICIANS WORK CLOSELY WITH RESEARCHERS TO DEVELOP STRATEGIES TO CREATE NEW APPROACHES THAT WILL MAKE CAR-T THERAPY SAFER AND MORE ACCESSIBLE. OUR ROBUST CLINICAL TRIALS PROGRAM AND PROGRESS IN CELLULAR THERAPY CONTINUE TO FUEL THE SCIENCE AND TREATMENT ADVANCEMENTS FOR THOSE IMPACTED BY CANCER."
>
> **– Abhinav Deol, MD**

# RESEARCH AROUND McLAREN

**Oncology related research conducted at a Karmanos Cancer Institute (KCI) location or throughout the oncology service line must be reviewed and approved by the KCI Protocol Review and Monitoring Committee (PRMC) and all applicable Institutional Review Boards (IRB) prior to activation. A KCI investigator will need to be involved if research activity occurs at any of the KCI cancer center locations. Please contact Dr. Gerold Bepler (beplerg@karmanos.org) and Dr. Lawrence Flaherty (flaherty@karmanos.org) if you are interested in activating an oncology related clinical trial or research project.**

## U-M, KARMANOS CANCER INSTITUTE AND WAYNE STATE RECEIVE $9.2M GRANT FOR PROSTATE CANCER RESEARCH

**Collaborative projects will address key questions about how prostate cancer develops and how best to treat it.**

Michigan's elite cancer programs are joining forces to find new solutions for prostate cancer. The University of Michigan Rogel Cancer Center and the Barbara Ann Karmanos Cancer Institute at Wayne State University have received a prestigious $9.2 million grant from the National Cancer Institute (NCI.)

The grant is through the NCI's SPORE, or Specialized Program of Research Excellence, which funds collaborative, interdisciplinary translational cancer research. The Michigan Prostate SPORE will focus on critical questions regarding how prostate cancer develops, with projects designed to address major barriers and challenges in diagnosis, treatment and metastasis.

The Rogel Cancer Center first received a prostate cancer SPORE grant in 1995, one of the first in the country. It has been continuously funded since then, resulting in several landmark discoveries that have identified key genetic drivers of prostate cancer.

In this renewal, the U-M team reached out to Karmanos-WSU researchers to leverage the institutions' complementary strengths. U-M and Karmanos Cancer Institute are the only two NCI-designated comprehensive cancer centers in Michigan.

"With the Michigan Prostate SPORE, we hope to improve outcomes for men with prostate cancer by making scientific advances that address critical questions in how the disease develops and how best to treat it. The partnership between the Rogel Cancer Center and Karmanos Cancer Institute will help us find innovative solutions that ultimately benefit patients," says co-principal investigator Arul M. Chinnaiyan, MD, PhD, director of the Michigan Center for Translational Pathology and S.P. Hicks Professor of Pathology at Michigan Medicine.

Elisabeth Heath, MD, FACP, associate center director of Translational Sciences, leader of the Genitourinary Oncology Multidisciplinary Team at Karmanos, and professor of Oncology

at Wayne State University School of Medicine, is an active clinical and scientific member of Karmanos and the Patricia C. and E. Jan Hartmann endowed chair for Prostate Cancer Research.

"We are honored to collaborate with U-M on this prestigious NCI SPORE grant to continue the Michigan Prostate SPORE," said co-principal investigator Dr. Heath. "We are fortunate that our research at Karmanos highlights our diverse population, which will complement the work underway at U-M.

"Collectively, we have the opportunity to gain a better understanding of metastatic prostate cancer in many populations and discover additional ways to treat this disease, as well as prevent it."

The Michigan Prostate SPORE is centered on three projects designed to translate laboratory discoveries into clinical advances. Projects range from early detection to tackling the most aggressive and advanced form of the disease, called castration-resistant metastatic prostate cancer.

1. **Understanding a new subset of metastatic prostate cancer.** Dr. Chinnaiyan's lab has previously found 7% of metastatic prostate cancer patients have loss of the gene CDK12. This subset of tumors was produced more immune T-cells and laboratory studies suggest they may be responsive to immunotherapy checkpoint inhibitors, a treatment that has overall had limited success in prostate cancer. This project will focus on metastatic castration-resistant prostate cancer with CDK12 mutation, seeking to uncover new treatment targets or biomarkers and to perform clinical trials using immune checkpoint inhibitors.
2. **Using a urine test for early detection and high risk.** One of the biggest questions in prostate cancer is distinguishing between which tumors are slow-growing, requiring minimal intervention, and which are likely to be aggressive and need immediate treatment. This project will investigate a new urine-based test developed at U-M that looks at a combination of multiple prostate markers, genes and other risk variants. The goal is to improve early detection of prostate cancer in those at high genetic risk and to understand among those diagnosed with prostate cancer who needs aggressive treatment and who may benefit from a less-intensive approach.
3. **Overcoming treatment resistance.** The hormone androgen plays a key role in prostate cancer, with current treatment including drugs designed to block signals from the androgen receptor. The problem is, nearly all tumors become resistant to these therapies. This project will investigate a new way of targeting the androgen receptor's messenger RNA in the hopes that disrupting the signaling upstream could block any androgen receptor signaling in the tumor, essentially depleting all androgen receptor signaling.

"Each of these projects will help us better understand the molecular mechanisms of prostate cancer progression and will also have a major clinical impact on the diagnosis and treatment of patients as we translate laboratory discoveries to the bedside," says co-principal investigator Ganesh Palapattu, MD, Chair and George F. and Sandy G. Valassis Professor of Urology at Michigan Medicine.

SPORE grants involve both basic and clinical/applied scientists working together and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers. The objective for all SPOREs is to reduce cancer incidence and mortality and to improve survival and quality of life for cancer patients.

This project is funded through National Cancer Institute grant P50CA186786-06.

*(FROM TOP) Arul Chinnaiyan, MD, PhD, and Ganesh Palapattu, MD, from U-M's Rogel Cancer Center; and Elisabeth Heath, MD, FACP, from Karmanos Cancer Institute and Wayne State University, are co-principal investigators of Michigan Prostate SPORE.*

RESEARCH AROUND McLAREN

*(FROM TOP) Malcolm P. Cutchin, PhD, Felicity Harper, PhD, and Hayley Thompson PhD.*

# KARMANOS CANCER INSTITUTE AND WAYNE STATE UNIVERSITY RECEIVE $3.1 MILLION NIH GRANT

African Americans have the lowest survival rate of any racial or ethnic group in the United States for most cancers – a problem that is magnified in southeast Michigan. These differences are often due to socioeconomic disparities that result in unequal access to medical care, health insurance, healthy food and more. African Americans who survive cancer also have the shortest survival of any racial/ethnic group in the United States for most cancers, according to the American Cancer Society.

A team of researchers from Wayne State University and the Barbara Ann Karmanos Cancer Institute are investigating the combined role that community, interpersonal and individual influences have on the health-related quality of life for African American cancer survivors, and how those influences create racial health disparities between African Americans and white survivors. The team includes Felicity W.K. Harper, PhD, associate professor of oncology in the Wayne State School of Medicine and the Karmanos Cancer Institute; Malcolm P. Cutchin, PhD, professor in the Institute of Gerontology and the Department of Health Care Sciences in Wayne State's Eugene Applebaum College of Pharmacy and Health Sciences; and Hayley Thompson, PhD, associate center director, Community Outreach and Engagement, Karmanos Cancer Institute and professor of Oncology, WSU School of Medicine.

The study, "ARISE: African American Resilience in Surviving Cancer," is a five-year, $3.1 million project funded by the National Cancer Institute of the National Institutes of Health that aims to identify targets of change and inform the development of interventions to address causes of poorer health-related quality of life experienced by African American cancer survivors.

The study aims to recruit 600 African American cancer survivors living in metropolitan Detroit. The team will work to create a theoretically and community-grounded model of variability in health-related quality of life in African American survivors. They will evaluate the success of the collaboration with a systematic evaluation of community stakeholders' perceptions of – and attitudes toward – the collaboration experience. They will also collaborate with community stakeholders to disseminate study findings to scientific and lay audiences, translate study findings, and inform future interventions.

"Our team is thrilled to have this unique opportunity to better understand how the cancer experience affects African American people in the tri-county area," said Dr. Harper. "While there has been much research on how white cancer survivors experience cancer, there is comparatively little study of African Americans and how factors unique to this community may influence their quality of life after cancer. With this NIH grant, we will have an unprecedented opportunity to explore how individual health and race- and neighborhood-related factors such as medical mistrust, neighborhood poverty and segregation may affect longer-term outcomes for this population. We look forward to partnering with the local community both in conducting this groundbreaking research and designing interventions to improve quality of life for African American cancer survivors."

This study is innovative because it will involve community stakeholders in aspects of the work typically limited to academics.

"We will review and revise our conceptual model in partnership with Karmanos Cancer Institute's Cancer Action Council network," said Dr. Thompson. "The councils are groups of cancer survivors, caregivers and advocates around Southeast Michigan who have received training in research methods and use their own local expertise to strengthen our efforts to reduce the region's cancer burden. We believe this is an important step toward health equity."

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# SCHOLARLY PROJECT STAGES EXPLAINED, PART 1

McLaren's Division of Scholarly Inquiry in its efforts to encourage, promote, and support scholarly activity among residents/fellows and teaching physicians developed a scholarly project stages diagram/flowchart (Figure 1) over two years ago. Over these past two years, it has been modified in response to suggestions and recommendations from residents/fellows and teaching physicians. The updated diagram/flowchart should serve as the roadmap for scholarly activity from its conception to its IRB/SARC approval. Even when residents/fellows, teaching physicians, and PhDs are aware of this diagram/flowchart, some misunderstanding seems to exist. Part 1 of this series, we will describe and explain the aim and purpose of the first three stages of the Scholarly Project Stages diagram/flowchart (Figure 1 blowout section).

**Step 1 – Research question.** Every scholarly activity project begins with a research question. The aim of this step is for residents/fellows to come up with a research question and do a brief literature review. The purpose of this literature review is to determine if that research question has been answered and to what extent because the main purpose of research is to contribute to increase the knowledge on a field of study. To do this, there should be unanswered aspects (i.e., knowledge gaps) of a research question (Step 1). If the research question has been answered or the subject matter extensively studied, the resident/fellow should come up with another research question. Otherwise, the resident/fellow moves to the next stage of the diagram/flowchart.

**Step 2 – Brainstorming.** The aim of the next stage in the process is to brainstorm, with a PhD and a teaching physician, about the feasibility and merit of the proposed research question. The purpose of this brainstorming session it to determine the scientific, clinical, logistic, financial, and overall feasibility of the proposed research question. At this stage, the resident/fellow should receive both clinical (teaching physician) and methodological (PhD) feedback and suggestions regarding his/her research question (Step 2). In addition, the research question should become more specific and its reach narrowed/focused given the time and resources available to the resident/fellow. If answering the proposed research question is not feasible because of one or more of the criteria mentioned above, the resident/fellow should come up with another research question (start over the process). If everyone agrees that the study is clinically and scientifically

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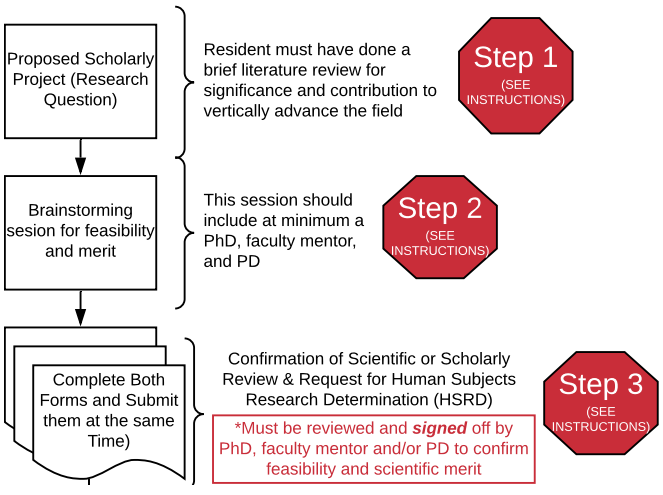



## FACULTY, FELLOWS & RESIDENTS
### SCHOLARLY ACTIVITY NEWS

**Carlos F. Rios-Bedoya, ScD**

***In Part 2 of this series I will describe and explain the aim and purpose of the diagram/flowchart if the scholarly project is determined by the IRB as Human Subjects Research. The diagram/flowchart presented and discussed in this article is available upon request to a PhD. In the Division of Scholarly Inquiry, we have a commitment and responsibility to promote, expedite, facilitate, and support scholarly activity productivity among McLaren residents, fellows, and teaching physicians. For additional information or questions contact Dr. Carlos F. Ríos-Bedoya at carlos.rios@mclaren.org***

FACULTY, FELLOWS & RESIDENTS
**SCHOLARLY ACTIVITY NEWS**

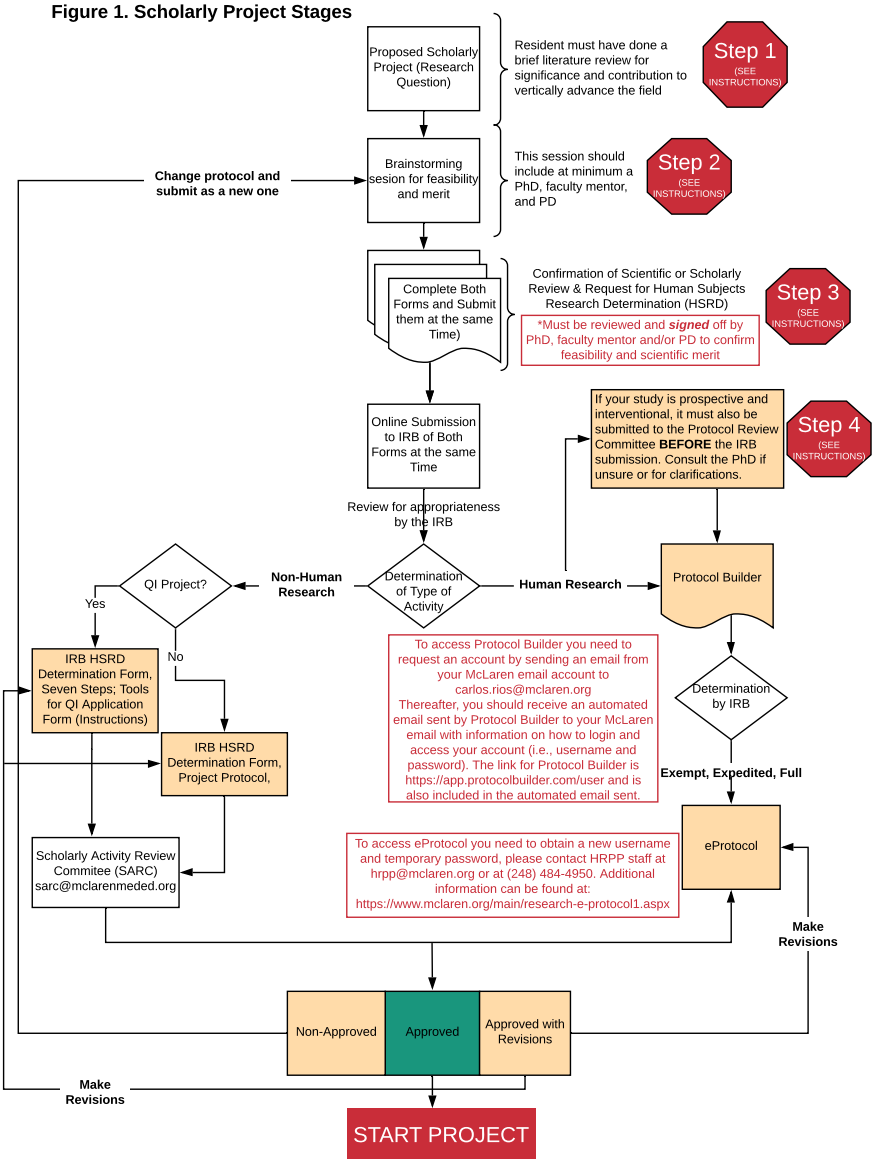
# SCHOLARLY PROJECT STAGES EXPLAINED

*CONTINUED FROM PAGE 11*

meritorious and feasible, the resident/fellow moves to the next stage of the diagram/flowchart.

**Step 3 – IRB Forms.** The next stage of the process requires the interaction of the resident/fellow with the McLaren Institutional Review Board (IRB) for the first time. The aim of this stage is for the resident/fellow to complete the required forms and submit them to the IRB. The purpose of this stage is for the resident/fellow, under the guidance of the PhD and teaching physician, to electronically submit the Human Subjects Research Determination (HSRD) form and the Confirmation of Scientific or Scholarly Review for Validity form to the IRB requesting human subjects determination of the proposed scholarly project and acknowledgement of scientific or scholarly review (Step 3). After the resident/fellow completes these forms, they should be reviewed and signed by a PhD and a teaching physician prior to submission. Once these forms are signed and electronically submitted together, residents/fellows should wait for the IRB determination before moving forward with their scholarly project.

**Figure 1. Scholarly Project Stages**



EQuIP CORNER

# HUMANITARIAN USE DEVICE: AN OVERVIEW

## Background

Challenges arise in the treatment of rare diseases or conditions occurring in small groups of targeted patients, while gathering valid scientific evidence to support the safety and effectiveness of treatments.

The Humanitarian Use Device (HUD) program was established in 1990 along with the passage of the Safe Medical Devices Act. The purpose of this program was to create an alternative pathway to obtain market approval for medical devices that may help people with rare diseases or conditions. A HUD designation is obtained through the FDA's Office of Orphan Product's Development (OOPD).

The Humanitarian Use Device is defined in 21 CFR 814.3 (n) as a device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year. That number of 8,000 was increased from 4,000 in **2016**, with the 21st Century Cures Act with the purpose of encouraging the discovery and use of these devices.

Once a HUD designation is granted, a Humanitarian Device Exemption (HDE) application can be submitted to the FDA's Center for Devices and Radiologic Health (CHRH) or Center for Biologics Evaluation and Research (CBER). The HDE application is the second step in seeking marketing and shipping authorization for a HUD.

However, distribution of an HDE is limited to those sites ensured by the HDE holder to have functioning Institutional Review Board (IRB) oversight. The Humanitarian Device Exemption criteria states there is no comparable, legally marketed device already available. The HDE is exempt from the effectiveness requirements of sections 514 and 515 of the FD&C Act. To qualify, a device must meet the following criteria:

1. The device will not expose patients to unreasonable or significant risk of illness or injury, and the probable benefit to health from use of the device outweighs the risks. This considers the probable risks and benefits of currently available devices or alternative forms of treatment;
2. The device would not be available to a person with the disease or condition in question without the HDE, and no comparable device is available to treat or diagnose this disease or condition; and
3. The device is designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the US on an annual basis.

*Research or efficacy data Is not required for an HDE.* Potential, probable, benefits of the device outweigh its risks. The FDA recognizes that in some instances there may be little or no clinical experience with the device that is the subject of an HDE application. The HDE holder is responsible for

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***REFERENCES:***

*FDA Regulations:*
*21 CFR 814.110, 21 CFR 814.100 (d), 21 CFR 56.104 (c)*

*MHC Policies:*
*MHC_RP0120: Humanitarian Use Device*
*MCH_RP0119-Expanded Use of Investigational Drugs and Devices*

# HUMANITARIAN USE DEVICE: AN OVERVIEW

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maintaining records of the name and addresses to which the HUD is shipped, submitting annual reports to the FDA, including safety events. The HDE cannot be sold for profit, except in narrow circumstances.

### There are generally four types of uses for HUDs:

1. Treatment or diagnosis under an HDE for the HUD's approved labeling and indication(s): i.e. in Medical Practice. This type of use is **not** considered a research activity; however federal regulations require **IRB approval** (21 CFR 814.124): "A HUD may be administered only if such use is approved by an IRB." The HDE holder is responsible for ensuring that a HUD under an approved HDE is administered only in facilities having IRB oversight. This is blanket approval per institution. Individual patient approval not required.
2. Clinical investigation (i.e., collection of safety and effectiveness data) involving a HUD, whether for its HDE-approved indication(s) or for a different indication. This type of activity is considered research. As such, **prospective IRB approval is required**. Prior to HDE approval, any studies using the device must be under IDE regulations (21 CFR part 312) and must have IRB approval.
3. Treatment or diagnosis under an HDE for an **off-label** or **compassionate use** of the HUD. If a physician in a non-emergent situation determines that there is no alternative device for the patient's condition, and the condition is serious, the HUD may be used off-label. This use requires prior FDA and prior IRB approval before the device is used. (21 CFR 312.300). This type of use allows access for patients who do not meet the requirements for inclusion in the clinical investigation but whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition.
4. Emergency Use of a HUD. A HUD is used in an emergency/life threatening situation to prevent serious harm or death to a patient when standard acceptable treatment is not available, and when there is not time to secure IRB approval. **This use is off-label and has not been approved by the FDA, and consequently, the IRB for this indication.** There may be a situation when an investigational device that is intended for research is used in an institution without IRB approval for the device, or for the approved indication. This would also constitute emergency use.

**ACRONYMS**

**IDE: Investigational Device Exemption: exemption allows sponsor to ship investigational (unapproved, investigational) device**

**HUD: Approval based on evidence of safety and probable benefit. Requirement to establish reasonable assurance of effectiveness waived.**

**HDE: Humanitarian Device Exemption: exemption from effectiveness requirements imposed on IDEs. Once granted, is now an approved device (not investigational) – allows HUD to be marketed.**

There is debate surrounding use of an IRB approved HUD in an emergency for its approved indication vs. its non-approved indication. Regulations concerning emergency use of a HUD do not clearly differentiate between IRB approval of the FDA approved indication vs. a non-approved indication. A HUD is approved for use by the FDA for its approved indication only because it has only determined safety and probable benefit for this use. Similarly, an IRB approves use of the HUD in the institution for its approved use.

Is "emergency use" and "off label" use the same? They can be. Remember, essentially all HUD use can be emergent. The difference is as to whether it is used for the approved indication or "off label". If it's used for its approved indication, it is not true "emergency use" in this context.

### Emergency use requires the following conditions be met:

1. The patient has a life threatening or severely debilitating disease or condition; and
2. There is no standard or generally recognized alternative treatment options with an equal or greater likelihood of treating the patient's condition; and
3. The patient's condition requires immediate intervention before review by the IRB is possible to avoid major irreversible morbidity or death.

In addition to the above, the treating physician must obtain an independent physician assessment from an uninvolved physician for concurrence of HUD use. Importantly, no other reasonable alternatives must exist.

Per FDA regulations, permission for Emergency Use may be granted one time per institution for one patient under the three conditions listed above. If any of the above three conditions do not apply, **or if there is a desire to use the test article again** on the same patient or different patient, an IRB application must be submitted for review and approved by a convened IRB. The FDA mandates an institution's IRB to further define their area of approval. In other words, it is the IRB's prerogative to define the HUD approval within its institution.

**The regulation is not intended to limit the authority of a physician to provide emergency care, and subsequent emergency use should not be withheld.** However, if it appears probable that similar emergencies will require subsequent use of this HUD for an unapproved indication, every effort should be made to develop a protocol for future use.

If a HUD is used in an emergency for its unapproved indication, the IRB needs to be notified within **5 working days**. If this HUD is used again in this institution for another unapproved indication, then it must be presented to a convened IRB. Of course, we don't always know if this device will possibly need to be used in the future right? Sometimes there might be an inkling that the HUD will possibly need to be used. If it happens again, then we must bring this to the IRB for review.

### The IRB's Responsibilities:

- Initial full board review by a convened IRB
  - Review the risks to patients that are found in the product labeling
  - Ensure the risks are minimized, and
  - Evaluate whether the risks are reasonable in relation to the proposed use of the device
- Review FDA approved indications
- Determine if informed consent is necessary
- Provide continuing review

### Physician Responsibilities to the IRB:

- Submit the initial application to the IRB via e-protocol
- Provide documentation verifying the device/sponsor has been granted an FDA-approved HDE for use of the device
- Provide the IRB with any amendments or supplements to the HDE
- Submit annual reports from the HDE holder
- Submit HUD brochure and/or patient information packet
- Submit Continuing review application to the IRB
- Submit reports to the FDA, IRB, and the HDE holder for subject death or serious injury
- Submit emergency off label use to the IRB within 5 days
- Notify the IRB if future off label use is anticipated

In conclusion, HUD's are essential to treating certain rare conditions and diseases. These devices are intended for our physicians to use. However, IRB oversight and approval are required due to the limitations of safety and effectiveness data. Our subject's wellbeing is contingent on our governmental agencies and intuitional IRB's providing this oversight.

## BROWN BAG SERIES

**HUD/HDE's: An Overview**
**December 10, 2019 12:00-12:45**
**LIVE WEBINAR**

**Alternative Consenting: E-Consenting and Telemedicine**
**March 10, 2020 12:00-12:45**
**LIVE WEBINAR**

***To register contact Marybeth McCarthy at (248) 484-4987 or Marybeth.mccarthy@mclaren.org.***

## UPCOMING RESEARCH EDUCATION

**ACRP 2020**
**Seattle, WA**
**May 1-4, 2020**

**2020 AAHRPP Annual Conference**
**Baltimore, MD**
**May 19-21, 2020**

**2020 SOCRA Annual Conference**
**Las Vegas, NV**
**September 25-27, 2020**

# ANNOUNCEMENTS AND WHAT'S NEW

Katie Pittel, JD

Congratulations **Katie Pittel, JD**, IRB Analyst, for passing the Certified IRB Professional (CIP) Exam. Certified IRB Professional (CIP) certification is granted from the organization Public Responsibility in Medicine and Research (PRIM&R). It is for individuals working with IRBs. The CIP credential was developed by PRIM&R to promote ethical research practices and programs by ensuring that professionals charged with their administration have demonstrated an advanced level of knowledge, understanding, and experience.

The CIP certification program was created in 1999 after many years of discussion and planning. The program was the result of a broadly based, grassroots effort by IRB professionals and policy makers committed to improving the quality of HRPPs. More than 3,000 individuals have become certified since the credential was introduced. PRIM&R is proud that this voluntary program has been so widely embraced by the HRPP community as a means to advance and demonstrate competence in such an important field.

## RESEARCH AROUND KARMANOS
## KCI AND WAYNE STATE

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The paths through which race-related community, interpersonal and individual domains of influence may affect the health-related quality of life of African American survivors has not been comprehensively studied, nor has there been a strong community engagement to develop and test a social-ecological model with follow-up to disseminate study findings with the community.

"With this award, we have the unique opportunity to assess various levels of factors that potentially affect the quality of life for African American cancer survivors," said Dr. Cutchin. "Those factors range from neighborhood conditions to experiences of racial discrimination to personal optimism. I'm very excited to work with this team and have a chance to inform future interventions for this population."

The grant number for this National Cancer Institute project is 232514-01.

## NEW IRB SOFTWARE SYSTEM COMING!

The Research Integrity Department will be introducing a new IRB management software system to replace eProtocol. In the upcoming months you will receive more information on the training schedule and the planned "Go Live" date for the new software. Stay tuned!

## RESEARCH AROUND McLAREN
## CAR-T THERAPY

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chemotherapy treatments. In diffuse large B-cell lymphoma, following CAR-T therapy, the response rate is around 70-80 percent, with long-term remission in the 40 to 50 percent range. For leukemia patients, initial response rates of 80-90 percent have been reported. The goal of CAR-T therapy is to put the patient's disease in long-term remission and we hope to see continued remissions with this therapy as more data becomes available.

CAR-T cell therapy is very promising and further research is ongoing to develop this approach to target other types of cancers. Our experienced team at Karmanos is working with other investigators to address and overcome some of the challenges associated with this therapy.

Currently, CAR-T treatments are customized for each patient using their own cells. This process takes time, which can be crucial for the patient needing this treatment. In addition, insurance authorization can take some time.

As a National Cancer Institute-designated comprehensive cancer center, our clinicians work closely with researchers to develop strategies to create new approaches that will make CAR-T therapy safer and more accessible. Our robust clinical trials program and progress in cellular therapy continue to fuel the science and treatment advancements for those impacted by cancer.

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