RESEARCH *Matters*

WINTER 2021

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

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RESEARCH AROUND McLAREN

MCRI EXPANDS RESEARCH TO McLAREN OAKLAND

McLaren Center for Research and Innovation (MCRI) is proud to announce the opening of a new clinical trials office at McLaren Oakland. Dr. Franklin Rosenblat, infectious disease physician at McLaren Oakland, recently began enrollment in McLaren's first inpatient COVID-19 Phase II drug trial, along-side Dr. Christopher Provenzano at McLaren Macomb and Dr. John Youssef at McLaren Flint. The Grifols sponsored trial is evaluating high dose Intravenous Immune Globulin (IVIG) plus standard medical treatment for certain COVID-19 patients requiring Intensive Care.

In order to support this enormous effort, MCRI is providing part-time research coordinator support to the site, and McLaren Oakland has generously provided space and equipment needed to operationalize the office. In opening our first trial at this institution, we have encountered outstanding support from local departments such as pharmacy, laboratory, critical care nursing and administration. A Phase II inpatient clinical drug trial is an extremely demanding undertaking for everyone involved. McLaren Oakland staff have shown a strong commitment to providing this treatment option to their patients, prioritizing the work that needs to be done to open the trial on an accelerated timeline, with an already heavy workload.

Margaret Dimond
PRESIDENT AND CEO
McLAREN OAKLAND

MCRI graciously thanks the team at McLaren Oakland for the extra time and effort put forth to support this new clinical trials office and the first open and enrolling trial at this institution. We look forward to providing more research opportunities for the McLaren Oakland patient population in the near future.

Margaret Dimond, President and CEO of McLaren Oakland, was instrumental in securing space and resources for MCRI's new office. "On behalf of McLaren Oakland we are thrilled to be able to engage in meaningful research, especially around COVID studies," expressed Ms. Dimond. "Oakland has been engaged in medical education as a part of its mission. To add research is a natural progression. Thank you to the physician and clinical staff who advocate for clinical and translational studies!"

MCRI GRACIOUSLY THANKS THE TEAM AT McLAREN OAKLAND FOR THE EXTRA TIME AND EFFORT PUT FORTH TO SUPPORT THIS NEW CLINICAL TRIALS OFFICE.

If you are a physician at McLaren Oakland and would like to participate in a clinical trial, please contact the McLaren Center for Research and Innovation at (248) 484-4960 or MCRI@mclaren.org

COVID-19 PANDEMIC BRINGS NEW INVESTIGATORS TO MCRI

As the COVID-19 pandemic began to swell in April 2020, McLaren Center for Research and Innovation (MCRI) quickly shifted gears towards research opportunities that could provide different treatment options for our many affected patients. This shift garnered interest from several physicians across the system who had never participated in research at McLaren. Elizabeth Pionk, DO, Hospitalist at McLaren Bay Region, quickly expressed interest in the COVID-19 Convalescent Plasma Expanded Access Program. Dr. Pionk explained her immediate interest in the program, "Through participation in research, we are able to evaluate the effects of treatments. When the COVID-19 pandemic started, my colleagues and I saw research as an opportunity to improve the treatment knowledge, strategies, outcomes, and lives of our patients. With little known about COVID-19 at that time, I wanted to help evaluate safe and effective treatments for our patients and communities. The progress we have made will have positive effects on current and future treatments and ultimately improve patient care and outcomes."

Elizabeth Pionk, DO

Dr. Pionk enrolled several of her patients into the convalescent plasma program and was diligent and responsive to the needs of the data collection effort that followed. As more COVID-19 research trial opportunities arose, it was natural to seek out a Principal Investigator with experience in COVID research and an interest in taking on the extra commitment that comes with it. The COVID-PACT trial with the TIMI Study Group out of Brigham and Women's Hospital was the perfect opportunity for Dr. Pionk to spread her wings and take on oversight of a trial for the first time. COVID-PACT is a Phase IV study looking at prevention of arteriovenous thrombotic events in critically ill COVID-19 patients. "Over the previous months, our team has treated numerous COVID-19 patients. We have witnessed the devasting effects of the virus, including arteriovenous thrombotic events," Dr. Pionk noted. "When the opportunity presented to have McLaren Bay participate in the COVID-PACT trial, we quickly jumped to join. Research and innovation during these unprecedented times will positively impact the treatment of COVID-19 patients and decrease the negative, life-long effects of the virus."

Being new to research, Dr. Pionk relies heavily on the local research coordinator for support. "Kate [Butler], has been a phenomenal resource and guide throughout this process," says Dr. Pionk. "She is truly an asset for our patients and community." Conducting a clinical trial can be daunting for a first-time investigator and MCRI has resources to help. Clinical trial operations are multi-faceted and require skilled and experienced administrators and coordinators to keep it all running smoothly. Six McLaren subsidiaries have a MCRI office and coordinator support: Bay Region, Flint, Greater Lansing, Northern, Macomb and Oakland. These coordinating sites are all managed centrally from the Research Administration office in Auburn Hills.

MCRI is receiving and reviewing numerous new COVID study opportunities each week. "It has been challenging to find investigators as our physicians and hospital departments are so busy with the high-acuity COVID-19 patients. The interest is there, but being an investigator takes extra time and effort that many don't have to give right now," explained Pam Wills-Mertz, Corporate Director of McLaren Center for Research and Innovation.

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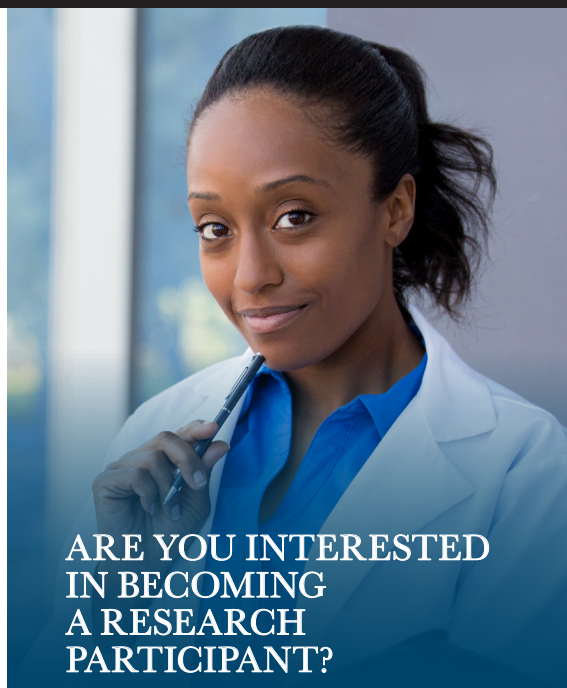

ARE YOU INTERESTED IN BECOMING A RESEARCH PARTICIPANT?

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**
- **COVID-19**
- **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

Bharath Naravetla, MD

McLAREN HIGHEST ENROLLER IN THE WORLD FOR ASSIST STUDY

Congratulations to neurointerventionalist Dr. Bharath Naravetla on his leadership in the ASSIST Registry. McLaren has been named the highest enrolling site in the world, according to the latest study newsletter from Stryker. Dr. Naravetla, Dr. Aniel Majjhoo, and Dr. Mahmoud Rayes have enrolled a combined 73 patients to date, making the monthly enrollment rate more than 5.7 patients per month. There are approximately 55 other sites around the world conducting this registry study. We applaud Dr. Naravetla and his study team for this outstanding effort and accomplishment!

MCRI OFFERS RESEARCH FUND MANAGEMENT SUPPORT

Any investigator that is submitting for grant funding should reach out to MCRI for assistance in managing the funds. All grant submissions must be approved prior to submission to the granting agency. Please email the grant proposal to the attention of the Corporate Director of McLaren Center for Research and Innovation at MCRI@mclaren.org. Please allow 5 days for review prior to agency deadline. This department will also support financial management of the grant monies, once received.

McLAREN RESIDENT RECEIVES BCBSM FOUNDATION GRANT

Dr. Julie Thai of the McLaren Flint Family Medicine Residency Program has been awarded funding from the Blue Cross Blue Shield of Michigan Foundation. She received $10,000 to support her project, “Motivational Interviewing to Stop Smoking in Michigan Initiative” (MISSMI). Dr. Thai plans to conduct this research study with Dr. Jennifer Carty. The purpose of the study is to determine whether group-based, virtual motivational interviewing is an effective and sustainable intervention to help individuals successfully quit smoking.

KARMANOS RESEARCHERS PUBLISH ARTICLE IN 'NATURE REVIEWS CLINICAL ONCOLOGY'

Karmanos Cancer Institute is pleased to announce that the work of Ramzi Mohammad, PhD, member, Molecular Therapeutics Research Program, Karmanos Cancer Institute and Wayne State University School of Medicine (WSU SOM), and Asfar Azmi, PhD, co-leader, Tumor Biology and Microenvironment Research Program, Karmanos Cancer Institute and assistant professor, WSU SOM, has been published in a comprehensive review article in "Nature Reviews Clinical Oncology."

nature REVIEWS CLINICAL ONCOLOGY

This publication, which is co-authored by Hafiz Uddin, PhD, postdoctoral fellow, Department of Oncology, WSU SOM, continues their successful basic, translational and clinical research on nuclear protein transport pathways. The comprehensive article covers the biology of protein transport and the pre-clinical and clinical development of small molecule inhibitors that target this important protein. The article is published at: (https://pubmed.ncbi.nlm.nih.gov/33173198/)

This group has spent more than a decade researching the pre-clinical development of nuclear transport inhibitors. Their work was critical in developing Selinexor (XPOVIO), a drug that is now Food and Drug Administration (FDA)-approved for the treatment of cancer patients with relapsed or refractory multiple myeloma and non-Hodgkin's lymphoma. The drug was also introduced in a global COVID-19 clinical trial. Karmanos served as one site for the study. Selinexor is now being developed further under the Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP). Several national clinical studies are planned.

"Protein movement within cells is important for their normal function," explained Dr. Mohammad. "Such movement is guided by specialized carrier proteins or transporters. Exportin 1 or XPO1 is the major exporter of nuclear proteins. In cancer, XPO1 becomes hyperactive and displaces the tumor suppressors to the incorrect compartment, thereby inactivating their function. XPOVIO is a drug that blocks such transport and retains the tumor suppressors in the correct cellular compartment and allowing them to control tumor growth."

"This is a joint effort beginning from our basic science group, which was supported by collaborative pharma partner Karyopharm Therapeutics Inc., as well as clinical investigators at Karmanos who collectively helped move a concept from the lab to FDA approval. We continue to find ways to improve the efficacy of this drug through the discovery of novel combinations. There is a need to identify prognostic and therapeutic biomarkers that could guide a more tailored XPOVIO therapy and is currently being intensively investigated by our group," Dr. Azmi said.

In line with this project, the team is currently conducting correlative research on two active clinical studies at Karmanos. The first is a National Institutes of Health (NIH) Method to Extend Research in Time (MERIT) Award-funded study on pancreatic cancer. This study is being led by Philip Philip, MD, PhD, FRCP, leader, Gastrointestinal and Neuroendocrine Tumor Multidisciplinary Team (MDT) at Karmanos Cancer Institute, professor, WSU SOM. The second study is on non-Hodgkin's lymphoma and is led by Erlene Seymour, MD, member of the Malignant Hematology MDT, Karmanos Cancer Institute, assistant professor, WSU SOM,

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RESEARCH AROUND McLAREN

KARMANOS CANCER INSTITUTE LAUNCHES CLINICAL TRIALS STUDY INFORMATION PORTAL

Karmanos Cancer Institute is pleased to announce the launch of a new clinical trials study information portal (SIP) on Karmanos.org. This portal was launched on Monday, November 9, 2020.

The SIP website, which is integrated with OnCore Clinical Trials Management System, is used by medical professionals, researchers and the general public to search clinical trials recruiting at Karmanos. The site allows users to easily search, sort and navigate through the many clinical trials available at Karmanos Cancer Institute.

Features include:

- Principal investigator profiles
- Eligibility criteria from clinicaltrials.gov
- List of studies on related-physician profiles
- Location maps and phone numbers of study sites
- Search fields including cancer multidisciplinary team/type, investigational device, NCT ID and multiple search terms
- Mobile-friendly design (Note: The Karmanos Clinical Trials Mobile App will still be available).

Additional features are expected to go live in the coming months. To view the new portal, visit www.karmanos.org/opentrials.

“The launch of the clinical trials study information portal allows us to better serve our patients and creates greater ease for our physician partners and researchers as they explore Karmanos’ clinical trial offerings. We are proud to offer more than 800 clinical trials to give patients access to tomorrow’s care today. By creating an easier way to organize information about these trials, we can ensure that these treatments reach all patients who are eligible,” said Gerold Bepler, MD, PhD, president and CEO of Karmanos Cancer Institute.

The Barbara Ann Karmanos Cancer Institute has one of the largest and best clinical trial programs in the United States, giving patients better access to new cancer treatments. Our patients have access to more than 250 promising new cancer treatments often available only at Karmanos Cancer Institute. Karmanos has patients actively participating in more than 800 clinical trials, which are developed and sponsored by our own physicians and researchers, major pharmaceutical companies or national cooperative group programs funded by the National Cancer Institute (NCI).

This allows us to offer patients treatments that are often not available anywhere else. In fact, one-third of all new cancer drugs were developed with our participation in trials. As the state’s only hospital focused solely on cancer, we take our research role seriously while also delivering care with the utmost compassion and understanding. With our long-term partnership with the Wayne State University School of Medicine, we are committed to promoting excellence in cancer research, education and clinical care. To speed treatments from the laboratory to the patient’s bedside, our partnership represents a synergistic collaboration between the laboratory scientists, cancer experts and clinicians who interact directly with patients. Together, we have conducted research that has contributed substantially to therapeutic breakthroughs in cancer and that continues to define new standards of care.

KARMANOS CANCER INSTITUTE RECEIVES RENEWAL OF NATIONAL CANCER INSTITUTE (NCI) CORE GRANT

This renewal extends Karmanos' 42-year history of prestigious designation as one of only 51 Comprehensive Cancer Centers in the nation

The Barbara Ann Karmanos Cancer Institute is pleased to announce that its National Cancer Institute (NCI) Core Grant has been renewed. This renewal extends Karmanos' prestigious NCI designation through 2025. Karmanos is among 51 centers nationwide to receive this designation.

NCI-designated cancer centers are characterized by scientific excellence and the capability to integrate a diversity of research approaches to focus on the problem of cancer. They play a vital role in advancing towards the goal of reducing morbidity and mortality from cancer.

"This designation reaffirms what we see at Karmanos every day: that our researchers and clinical staff members are doing outstanding work in their fields," said Gerold Bepler, MD, PhD, president and CEO of the Barbara Ann Karmanos Cancer Institute. "Our NCI designation sets us apart in the fields of cancer research and treatment by showing our patients, colleagues and peers that we are committed to creating a world free of cancer. With this achievement, we are empowered to press forward in the fight against cancer."

To secure grant renewal, Karmanos submitted a 2,000-page application and underwent a site visit by a panel of experts from across the country. The 2020 visit took place virtually for the first time in history, due to the COVID-19 pandemic. This visit resulted in a detailed report including a score sheet. We are proud to report the work of Karmanos' Office of Cancer Health Equity and Community Engagement (OCHECE), which conducts community-based behavioral research, achieved a perfect score of "exceptional". Overall, Karmanos exceeded its standing from 2015 – a result that validates the hard work and dedication of the Karmanos team.

The NCI first designated the Barbara Ann Karmanos Cancer Institute as a comprehensive cancer center in 1978, when the Institute was called the Meyer L. Prentis Comprehensive Cancer Center of Metropolitan Detroit. It was the first center in Michigan to receive the NCI designation and remains one of only two in Michigan with this title.

To be designated as a comprehensive cancer center by the NCI, a center must:

- Demonstrate a depth and breadth of cancer research activities in each of three major areas: basic laboratory, clinical and prevention control in population-based science
- Be effective in serving their catchment area, as well as the broader population, through the cancer research they support and the cancer control activities they undertake
- Integrate cancer training and education of biomedical researchers and community health care professionals into programmatic efforts to enhance the scientific mission of the center
- Initiate and conduct early-phase, innovative clinical trials and participate in the NCI's cooperative groups by providing leadership and recruiting patients for trials
- Conduct activities in outreach and education and provide information on advances in health care for health care professionals and the public

Karmanos has met these criteria and is pleased to share highlights from our list of accomplishments. In the past five years:

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"The renewal of the Core Grant by the National Cancer Institute reinforces Karmanos Cancer Institute's status as one of the best cancer treatment and research operations in the mid-west and the largest in the state of Michigan. This renewal is the result of the hard work and dedication of our clinicians and researchers and enables us to provide bench-to-bedside medicine to our patients. We are grateful for the renewal of this NCI designation, as it allows us to provide critical resources and develop life-saving cancer treatments in the communities we serve. We can only imagine the continued advances in treatment protocols that will come from this achievement. No doubt, many lives will be saved."

– Philip A. Incarnati
President and CEO
McLaren Health Care

RESEARCH AROUND McLAREN

KARMANOS CANCER INSTITUTE AND WAYNE STATE UNIVERSITY APPROVED FOR A $149,324 ENGAGEMENT AWARD FOR PROJECT ON COVID-19

A team at Karmanos Cancer Institute and Wayne State University has been approved for a $149,324 funding award through the Eugene Washington Patient-Centered Outcomes Research Institute (PCORI) Engagement Awards program to support a new project: "Supporting Detroit Communities as Leaders and Partners in COVID-19 Research." The funds will support a COVID-19-related project enhancement to the previously funded and ongoing project, "Best Practices to Engage Black Men in the Development of a Cancer Health Equity Research Agenda."

The project is co-lead by Jinping Xu, MD, professor in the Department of Family Medicine and Public Health Sciences at Wayne State University, and Hayley Thompson, PhD, associate center director, Community Outreach & Engagement and faculty director of the Office of Cancer Health Equity and Community Engagement, Karmanos Cancer Institute, and professor in Department of Oncology, Wayne State University School of Medicine.

The project will focus on developing a community-informed COVID-19 research agenda and is currently recruiting members for two COVID-19 Action Councils. These groups will work to reduce COVID-19-related health disparities by engaging community members as partners in local COVID-19 research. Additionally, council members will have the opportunity to serve on a community research review board at Wayne State as part of a system to integrate community interests into research and ensure transparency. COVID-19 survivors, caregivers, essential workers, first responders and advocates from the metropolitan Detroit area are invited to apply. For additional information about the COVID-19 Action Councils and to access the application, visit karmanoscancerhealthequity.org/covid-19-action-council.

"We are thrilled to have this additional funding from PCORI to develop the COVID-19 Action Council so we may better understand the impact COVID-19 on our local communities and the necessary steps to reduce health disparities that have been exposed by COVID-19," said Dr. Xu.

"Traditionally, everyday people have been excluded from academic medical research, and community priorities and values are not typically considered. We're excited to work with our community partners – Detroit Parent Network, the Faith-Based Genetic Research Institute, LGBT Detroit and Community-Campus Partnerships for Health – to amplify community voices and perspectives on the COVID-19 research taking place in our city and region," Dr. Thompson said.

This COVID-19 project, as well as the original project, are part of a portfolio of projects that PCORI has funded to equip patients and other stakeholders to participate as partners in comparative clinical effectiveness research (CER) and disseminate PCORI-funded study results. Through the Engagement Award Program, PCORI is creating an expansive network of individuals, communities and organizations interested in and able to participate in, share and use patient-centered CER.

According to PCORI's Chief Engagement and Dissemination Officer Jean Slutsky, "This project was selected for Engagement Award funding because it will help the community increase their capacity to participate across all phases of the PCORI/CER process while responding to contextual changes as a result of the COVID-19 pandemic. We look forward to working with Wayne State University and Karmanos throughout their 2021 project."

Wayne State University's project and the other projects approved for funding by the PCORI Engagement Award Program were selected through a highly competitive review process in which applications were assessed for their ability to meet PCORI's engagement goals and objectives, as well as program criteria. For more information about PCORI's funding to support engagement efforts, visit pcori.org/content/eugene-washington-pcori-engagement-awards.

PCORI is an independent, nonprofit organization authorized by Congress in 2010 to fund comparative effectiveness research that will provide patients, caregivers and clinicians with the evidence needed to make better-informed health and health care decisions. PCORI is committed to seeking input from a broad range of stakeholders to guide its work.

COVID-19 PANDEMIC BRINGS NEW INVESTIGATORS TO MCRI

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"We reached out to Infectious Disease Specialists, Critical Care Specialists, and Pulmonologists for our COVID related Phase II drug studies, and have engaged a number of physicians who are now participating in clinical trials for the first time with MCRI," explained Pam Wills-Mertz, "It's exciting to work with new therapeutic areas, new physicians and spread awareness of the McLaren Center for Research and Innovation."

Becoming an investigator on a clinical trial is a process that involves additional training, certification, and extra time to devote to your coordinator, study patients and the study sponsor. Sponsors have rapid timelines and expect a high degree of attention and turn around on data entry and queries. With the help of MCRI and your local coordinator, together we can make this an exciting and rewarding addition to your medical career.

Please contact McLaren Center for Research and Innovation if you have questions or are interested in conducting a clinical trial at McLaren. MCRI@mclaren.org (248) 484-4950.

EQuIP CORNER

PROTOCOL DEVIATIONS VS. PROTOCOL VIOLATIONS: DEFINITIONS, REPORTING GUIDELINES, AND PREVENTION

By Andrea Klaver, MBA, CHRC

Confusion often exists surrounding the similarities or differences of a protocol deviation and a protocol violation. In fact, it continues to be one of my most-asked questions from different research communities throughout my time as a research compliance professional. In this edition of EQuIP Corner, we will review the differences between a violation and a deviation, identify ICH/GCP, Federal, and IRB reporting requirements for violations and deviations, and discuss actions that may help to prevent them from occurring in the first place.

It is important to note that the terms protocol deviation and protocol violation have different meanings and should not be used interchangeably. Although, a pattern of repeated protocol deviations of the same nature may constitute a protocol violation.

Protocol Deviations

A protocol deviation occurs when study activities diverge from the IRB-approved protocol without prior sponsor and/or IRB approval. Deviations may be considered a simple variance from the protocol, whether accidental or unintentional. Deviations do not increase risk or decrease benefit to the study subjects.

That is, deviations do not have a significant effect on (1) study subject's rights, safety, or welfare; and/or (2) the integrity of the study data. Examples of a deviation may include:

- A rescheduled study visit
- Failure to collect a supplementary self-report questionnaire
- Vital signs obtained prior to informed consent

Protocol Violations

A protocol violation occurs when there is divergence from the IRB-approved protocol (a deviation) that also (1) impacts a study subject's rights, safety, or welfare, (2) reduces the quality or completeness of the study data; or (3) affects the scientific integrity of the study. Violations generally increase risk or decrease benefit.

Violations may still be considered accidental or unintentional change to, or non-compliance with, the IRB-approved protocol. Examples of protocol violations may include:

- Inadequate informed consent (obtained informed consent on a non-date stamped form)
- Multiple visits missed or outside permissible windows
- Accidental use of prohibited medication or dose
- Enrollment of subjects not meeting the inclusion/exclusion criteria

Who is Responsible for Deviations and Violations?
Deviations and violations may result from the action of the study subject, study team, or other research staff. These individuals, along with auditors, monitors, regulatory staff, or other hospital staff are responsible for helping to assure protocol compliance and identify non-compliance.

Through the collaboration of these groups, a strong safety net is created to minimize the occurrence of deviations and violations. Is the informed consent re-affirmed before each visit, each procedure, and for each participant? Can we confirm the informed consent form is for the correct study, both before and after the consent process? Do the labs being drawn match what is in the IRB-approved protocol? These are just a few examples of instances within the study where we have the opportunity to strengthen the safety net.

Reporting Guidelines
ICH/GCP guidelines (Section 4.5 "Compliance with Protocol") state that "the investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and … approved by an IRB." Furthermore, the guidelines ask that investigators do not "implement any deviation from, or changes to, the protocol without agreement by the sponsor and … approval from an IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects."

In this guidance, the word "deviation" is used to convey the notions of both deviations and violations. Although, as discussed above, the terms should not be used interchangeably. Deviations by definition do not have a significant effect on a study subject's rights, safety, or welfare, so they will not inherently be used to eliminate immediate hazards or be reported as such. These situations are described and reported as violations.

The FDA does not distinguish between a deviation and a violation; all protocol variances are deviations. Here, the term deviation is not defined by either HHS (OHRP) human subjects regulations (45 CFR 46) or FDA human subjects regulations (21 CFR 50).

At McLaren, protocol violations must be reported to the IRB within 10 working days of the study team's knowledge of the occurrence. Protocol exceptions (a one-time enrollment of an individual who does not meet current IRB-approved criteria for inclusion in the research study as outlined in the protocol) require prior approval from the IRB and the study sponsor, if applicable, prior to the enrollment of the subject. Protocol deviations (an occurrence that does not meet the definition of exception or violation) are to be recorded by the investigator and submitted to the IRB at the time of the continuing review. For more information, see our Policy on Protocol Violations and Exceptions MHC_RP0122.

Reducing Deviations and Violations
Reducing protocol deviations and violations in the first place can save a lot of time and energy down the road. We may not be able to prevent them all, but there are steps we can take to minimize their impact on studies.

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UPCOMING RESEARCH EDUCATION

2021

SOCRA
Please visit the SOCRA Events Calendar at https://www.socra.org/conferences-and-education/events-calendar/ for virtual continuing education and training opportunities

MAGI's Clinical Research Conference – Spring
ONLINE
April 26 – 29, 2021
and May 3 – 6, 2021

ACRP 2021
Innovation in the Era of COVID
January 12 – 14, 2021

Operational Efficiencies
May 13, 20 and 27, 2021

Regulatory Trends and Compliance
September 16, 23 and 30, 2021

BROWN BAG SERIES

Upcoming Brown Bag webinars will be announced in early 2021

For more information, contact Andrea Klaver at (248) 484-4987 or andrea.klaver@mclaren.org.

FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

Carlos F. Rios-Bedoya, ScD

USMLE STEP 3:

BIOSTATISTICS & EPIDEMIOLOGY/ POPULATION HEALTH & INTERPRETATION OF THE MEDICAL LITERATURE

The COVID-19 pandemic has impacted the timeline for residents to take the United States Medical Licensing Examination (USMLE) Step 3. Furthermore, McLaren has delayed and granted extensions on its requirement for current first- and second-year residents for when to take and pass the USMLE Step 3. One content area that residents are not expecting is the Biostatistics & Epidemiology/ Population Health & Interpretation of the Medical Literature and the format of its questions. Some McLaren residents that have taken Step 3 have made comments regarding how "horrible" and how many of these related questions the exam had. Given that this content area is not a clinical one, residents are unfamiliar with the content of the questions and also their format. In this edition of *Research Matters*, I will provide examples of three different types of questions commonly found in Step 3 about this content area using information from a publicly available practice exam found in the USMLE website. The objective is for residents to become familiar with these types of questions and their format.

The first type of question is about epidemiology/biostatistics and follows a usual format.

A study is being conducted to assess mesothelioma in shipyard workers. A large shipyard firm has provided asbestos exposure records of all employees during the past 50 years. The health insurer for the workers has provided claims data that documents all chest x-rays and diagnoses of mesothelioma among current workers and retirees. The study enrolled shipyard workers who were diagnosed with mesothelioma and shipyard workers who were not diagnosed with mesothelioma. All subjects in the study had to have chest x-rays. Which of the following is the best rationale for selecting a comparison group that had chest x-rays?

A. Address confounding
B. Demonstrate causality
C. Minimize ascertainment bias
D. Reduce recall bias

There is not much unusual about the subject matter. Knowledge and understanding of these concepts are needed to correctly choose the right answer (C).

The next type of question deals with the interpretation of the medical literature. For this purpose, the USMLE provides an abstract of a published article follow by 2-3 questions about the abstract.

Question

In patients with cirrhosis and acute bleeding esophageal varices, how do endoscopic sclerotherapy and emergency portacaval shunt compare for control of bleeding and survival?

Methods

Design: Randomized controlled trial (San Diego Bleeding Esophageal Varices Study). ClinicalTrials.gov NCT00690027.

Allocation: Concealed.

Blinding: Blinded (gastroenterologist who evaluated patients for portal-systemic encephalopathy).

Follow-up period: Up to 17 years.

Setting: University of California San Diego Medical Center.

Patients: 211 patients (mean age 49 years, 77% men) with acute bleeding esophageal varices resulting from cirrhosis, who required a transfusion of ≥ 2 units of blood and, for patients transferred from other hospitals, observation of upper gastrointestinal bleeding within 48 hours of transfer. Exclusion criterion was > 1 previous session of endoscopic sclerotherapy.

Intervention: Endoscopic sclerotherapy (n = 106) or emergency portacaval shunt (n = 105). Emergency portacaval shunt comprised a direct side-to-side or direct end-to-side portacaval shunt done within 8 hours of initial contact.

Outcomes: Control of bleeding at > 30 days, survival, readmissions for variceal or nonvariceal bleeding requiring transfusion of packed red blood cells, and recurrent portal-systemic encephalopathy.

Patient follow-up: 100% (minimum follow-up until death or 9.4 years).

Main results: 15-year survival was lower with endoscopic sclerotherapy than with emergency portacaval shunt (10/106 vs 48/105, relative benefit reduction 79%, 95% CI 62 to 89; number needed to harm 3, CI 2 to 4). Other main results are shown in the Table.

Conclusion: In patients with cirrhosis and acute bleeding esophageal varices, emergency portacaval shunt was better than endoscopic sclerotherapy for control of bleeding, recurrent encephalopathy, and survival.

Endoscopic sclerotherapy (EST) vs. emergency portacaval shunt (EPCS) in patients with cirrhosis and acute bleeding esophageal varices

Outcomes	Child-Pugh Risk Class	EST	EPCS	P Value
Control of bleeding at > 30 days*		20%	100%	<.001
Median survival (years)	A	4.62	10.43	.003
	B	2.61	6.19	<.001
	C	0.58	5.30	.005
Mean number of readmissions for variceal bleeding requiring packed red blood cell transfusion		6.8	0.4	<.001
Recurrent portal-systemic encephalopathy†		35%	15%	.001

** Excluding indeterminate deaths at 14 days from nonbleeding causes.*
† In patients who survived 30 days and left hospital

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A 52-year-old man with hepatic cirrhosis comes to the emergency department because of a 3-hour history of vomiting blood. Esophagogastroduodenoscopy confirms actively bleeding esophageal varices. Based on the abstract shown, the physician is considering an emergency portacaval shunt (EPCS) procedure rather than endoscopic sclerotherapy (EST). According to the results in the abstract, approximately how many patients must be treated with EPCS rather than EST to prevent one case of recurrent portal-systemic encephalopathy?

A. 1
B. 3
C. 5
D. 10
E. 16

Which of the following most strongly limits the generalizability of this study's findings?

A. The allocation was concealed
B. EPCS is available only at specialty centers
C. The follow-0up period was too short
D. The patients were not blinded
E. Unmeasured confounders were not controlled by the study design

Which of the following conclusions is most appropriate based on the results presented in the table?

A. The 95% confidence interval for the difference in survival between EPCS and EST for Child-Pugh class A patients includes 0 years
B. EPCS is more effective than EST in decreasing hospital readmissions for variceal bleeding requiring transfusion
C. The median survival after EPCS is statistically significantly less for Child-Pugh class C than for Child-Pugh class B
D. The randomization procedure was ineffective in decreasing bias in this study

This type of question requires you to read the abstract very quickly and answer the three questions that followed. The first question needs to calculate the number needed to treat. The second question deals with generalizability issues in the abstract. Finally, the third question asks for interpretation of data in the table.

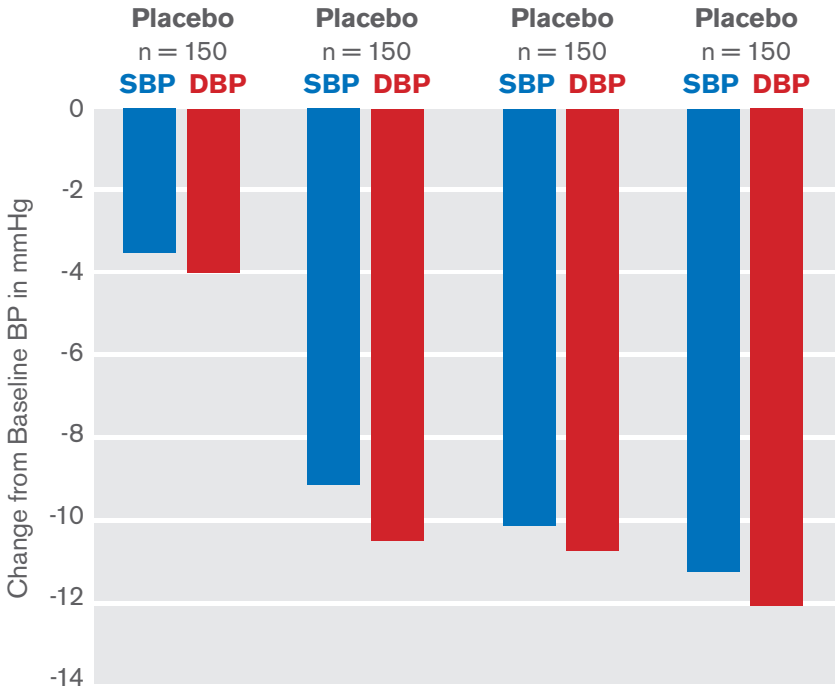
The third type of question commonly found in Step 3 is pharmaceutical ads and clinical and research inferences that can be made based on the information presented in the ad.

In the next page, an example of a pharma ad is presented followed by two questions related to the pharma ad. The pharma ad contains indications, dosage, warnings, side effects, contraindications, and research results. The first question asks about whether the medication should be prescribed to the patient described in the vignette. The second question asks to evaluate and interpret the graph in the ad showing the findings of a randomized control trial for the drug. Again, in this type of question it is needed to read an "external" source of information before proceeding to answer the actual question. In addition, clinical and non-clinical knowledge are evaluated through these pharma ads. In summary, these different types of question are trying to evaluate from exam takers their higher-level thinking process in a way residents might not be used to.

Essepro™ (Iesystoiol) Reduces Blood Pressure Significantly

In 2-month studies, Essepro therapy alone showed meaningful reductions in blood pressure[1]

Mean Reductions in Steering DBP and SBP from Baseline Trough Levels



P = >0.5 for all doses Essepro vs. placebo

Pooled date from two US and European phase II, 2-month, randomized, double-blind, placebo-controlled studies of Essepro monotherapy for treatment of mild to moderate hypertension. P = >.05 for all doses Essepro vs. placebo. The primary endpoint was lowest sitting systolic BP at trough. Mean values at baseline: sitting DBP at trough, 99.5 mmHg; sitting SBP at trough 153.8 mmHg (N = 1755, n = 1407).

In Clinical Studies Essepro demonstrated:

- Significant reductions in heart rate[2]
  - Heart rate decreased 6-9 BPM across all dosing groups[1]
- Further BP reductions when used in combination with other BP medication[1,2]
  - In a separate combination treatment study of Essepro with ACR's and/or diuretics
- Significant BP reductions in women
  - Similar BP reductions for women and men across dose groups
- Meaningful BP reductions in black patients[3]
  - In a separate 2-month study, therapy with Essepro alone showed statistically significant reductions but less than those reductions seen in non-black patients
  - Added BP reductions were seen when Essepro was combined with ACR's and/or diuretics

Essepro is a beta-adrenergic blocking agent indicated for the treatment of hypertension.

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FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

The Division of Scholarly Inquiry's goal is to provide the best possible training and education experience. We are available to hold virtual training sessions on practicing for Step 3. For more information or to schedule a training session contact Dr. Carlos F. Ríos-Bedoya (carlos.rios@mclaren.org).

Well-Tolerated at All Doses with Low Rate of Side Effects

Percentage of Adverse Events by Dose, Occurring More Frequently in Essepro™ than Placebo Patients, and in ≤1% of Patients

Adverse Event	Placebo n = 208 %	Essepro 1 mg n = 451 %	Essepro 2.5 mg n = 464 %	Essepro 5 mg n = 622 %
Dizziness	2	6	5	8
Headache	1	5	7	6
Fatigue	1	2	3	3
Nausea	1	0	2	2
Dyspnea	0	1	1	1
Chest Pain	1	0	2	1
Peripheral Edema	1	1	0	2
Bradycardia	0	2	0	1
Rash	0	0	1	1

Pooled date from three US and European phase II, 2-month, randomized, double-blind, placebo-controlled studies of Essepro in the treatment of mild to moderate hypertension (N = 2043, n = 1052).

Most side effects were mild and did not require discontinuation of Essepro[1]

- Most adverse events were assessed as mild by investigators and treatment was continued[1]
- Few patients discontinued treatment due to adverse events. 2.0% for Essepro vs. 2.1% for placebo[1]

No significant interactions with commonly used medications were observed[1]

- No significant interactions with hydro_____
- No significant interactions with hydro_____
- No significant interactions with hydro_____. The text on provided graphics was unreadable, so please provide something clearer text.

Important Safety Information

Patients treated with Essepro should be advised against sudden discontinuation of therapy. When discontinuing therapy, dosage should be gradually tapered over 2 weeks.

Essepro is contraindicated in patients with bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, severe hepatic impairment, and in patients who are hypersensitive to any component of this product.

Essepro should be used with caution in patients with peripheral vascular disease, renal impairment or thyrotoxicosis. Caution should be used in diabetics, as beta blockers may mask some manifestations of hypoglycemia.

In general, patients with bronchospastic disease should not receive beta blockers.

A 65-year-old woman comes to the office for blood pressure medication management. Medical history is significant for poorly controlled hypertension, psoriasis, and psoriatic arthritis previously treated with methotrexate. Additional medical history is significant for alcohol use disorder and elevated liver function tests. Medications include enalapril, spironolactone, and topical corticosteroids. Vital signs are normal except for a blood pressure of 160/104 mmHG. Physical examination discloses thick, scaly plaques on the scalp, buttocks, and upper and lower extremities. There are several spider antiomata on the chest and abdomen. The abdomen is distended and a fluid wave is noted. She has 2+ lower extremity edema. The patient says she would like to try a new drug called Essepro to treat her hypertension because she can get a 3-month supply of the medication for free.

Which of the following is the most appropriate response to the patient's request for the medication?

A. Essepro should be prescribed because she can get it for free
B. Essepro should not be prescribed because it can worsen her psoriasis
C. Essepro should not be prescribed because it is similar to her other medications
D. Essepro should not be prescribed because the patient has severe liver disease
E. Essepro should only be used for hypertensive emergencies

Which of the following interpretations can be made correctly from the graph on blood pressure reduction in the advertisement?

A. Blood pressure reduction from the three doses of Essepro cannot be compared to reduction with placebo because the number of patients on active drugs are higher than the number of patients on placebo
B. Doubling the highest dose of Essepro will decrease diastolic pressure from baseline by at least 15 mmHg.
C. The highest dose of Essepro should be used because it offers the greatest benefit
D. There is no clinically important difference in blood pressure reduction between the three dose groups
E. The significance of drug effect vs. placebo cannot be determined because of the low P value

KARMANOS RESEARCHERS PUBLISH ARTICLE

CONTINUED FROM PAGE 5

and Jeffrey Zonder, MD, leader of the Multiple Myeloma and Amyloidosis MDT, Karmanos Cancer Institute, and professor, Departments of Hematology and Oncology, WSU SOM.

"I am very proud that work done by our investigators on nuclear transport biology continues to bring success to this institution. Their tremendous work is emphasized by the publication of this high-impact article. I congratulate the Karmanos team for helping the development of a drug and for playing such a significant role in the FDA approval of Selinexor," said Gerold Bepler, MD, PhD, president and CEO of Karmanos.

In addition to the work conducted by Dr. Mohammad and Azmi's team, several other Karmanos investigators contributed to the development of the drug. These clinical investigators include Karmanos physicians Anthony Shields, MD, PhD; Elisabeth Heath, MD, FACP; and Ammar Sukari, MD.

FACULTY, FELLOWS & RESIDENTS

SCHOLARLY ACTIVITY NEWS

2020 PEER JOURNAL PUBLICATIONS

Alphabetical order by resident
Until 12/06/2020

**** Does not include StatPearls***

ENT

Colin Byrd, Douglas Kubek. Cervical chrondrocutaneous branchial remnant: A case report. Samira Ibrahim, Otolaryngology Case Reports. Volume 17, November 2020, 100241. https://doi.org/10.1016/j.xocr.2020.10024

Matt Mors, D.O. , Colin Bohr, D.O. , Michael Fozo, M.D. , Carl Shermetaro, D.O. Consultation Intervention Rates for the Otolaryngology Service: A Large Metropolitan Hospital Experience Spartan Medical Research Journal. Vol. 4, Issue 2, 2020.

Bowers ID, Imlay SP, Schroeder N, Bahu SJ. Retropharyngeal Osteolipoma Requiring an Interdisciplinary Approach. Ear Nose Throat J. 2020 Aug 30:145561320954131. doi: 10.1177/0145561320954131. Online ahead of print. PMID: 32862723

Hilton DB, Luryi AL, Bojrab DI, Babu SC, Hong RS, Bojrab DI 2nd, Santiago Rivera OJ, Schutt CA. Comparison of associated comorbid conditions in patients with benign paroxysmal positional vertigo with or without migraine history: A large single institution study. Am J Otolaryngol. 2020 Nov-Dec;41(6):102650. doi: 10.1016/j.amjoto.2020.102650. Epub 2020 Jul 15. PMID: 32702572

Keidar E, Bowers I, Sargent E. Mastoiditis Masquerade. Ear Nose Throat J. 2020 Aug 25:145561320950493. doi: 10.1177/0145561320950493. Online ahead of print. PMID: 32841094

Keidar E, Shermetaro J, Kwartowitz G. Pediatric Parotid Chronic Sclerosing Sialadenitis in an African-American Female: A Rare Case and Review of the Literature. Cureus. 2020 Jun 26;12(6):e8846. doi: 10.7759/cureus.8846. PMID: 32754389

Lofgren DH, Lenkeit C, Palanisamy J, Brown J. Mycoplasma Pneumoniae Induced Rash and Mucositis with Bilateral Otitis Media and Sinusitis. Cureus. 2020 Mar 28;12(3):e7449. doi: 10.7759/cureus.7449. PMID: 32351828 Free PMC article.

INTERNAL MEDICINE

Kaplan Jason .G., Kanwal A., Malek Ryan., Dickey J.Q., Keirn R., Zweig B., Minter D.

COVID-19 Resulting in Bilateral Pulmonary Emboli and a Right Ventricular Thrombus: Association or Causation? A Case Report. European Heart Journal Case Reports-published 10/2/20https://academic.oup.com/ehjcr/article/4/5/1/5917275

Kaplan Jason G, Kanwal A, Bahoora Justin, Berquist John, Hunyadi Victor, Keirn R. Papillary fibroelastoma presenting with multi-organ symptoms. J Community Hosp Intern Med Perspect. 2020;10(6):597-599. Published 2020 Oct 29. doi:10.1080/20009666.2020.1811067

https://www.tandfonline.com/doi/full/10.1080/20009666.2020.1811067

Kanwal A, Avgeropoulos D, Kaplan JG, Saini A. Idiopathic Purulent Pericarditis: A Rare Diagnosis. The American Journal of Case Reports. 2020 Feb;21:e921633. DOI: 10.12659/ajcr.921633.

Kanwal A, Kaplan J, Forst B, Patel B. Thrombus in transit raising suspicion for a hypercoagulable state. BMJ Case Rep. 2020 Oct 30;13(10):e235489. doi: 10.1136/bcr-2020-235489. PMID: 33127725; PMCID: PMC7604778.

ORTHOPEDIC SURGERY

Lerew S, Stoker S, Nallamothu S. The Rules of Four: A Systematic Approach to Diagnosing Common Musculoskeletal Conditions of the Knee. SMRJ. 2020;4(2).

Stoker, S., McDaniel, D., Crean, T., Maddox, J., Jawanda, G., Krentz, N., Best, J., Speicher, M., & Siwiec, R. (2020). Effect of Shelter-in-Place Orders and the COVID-19 Pandemic on Orthopaedic Trauma at a Community Level II Trauma Center. Journal of Orthopaedic Trauma, 10.1097/BOT.0000000000001860. https://doi.org/10.1097/BOT.0000000000001860

Jacob Best BS, Steven Stoker DO, Dalton McDaniel DO, Shawn Lerew , Gurkirat Jawanda, Neal Krentz, Mark Speicher, Ryan Siwiec. Effects of Easing Shelter-in-place Restrictions and the Lingering COVID-19 Pandemic on Orthopaedic Trauma at a Community level II Trauma Center. Accepted for publication in Orthopaedic Trauma Association International Journal.

CONFERENCE PRESENTATIONS

John Berquist, Jason Kaplan & Andrew Zazaian. Severe, symptomatic hypocalcemia due to denosumab and vitamin d deficiency in a post–menopausal female with osteopenia. 22nd European Congress of Endocrinology. Endocrine Abstracts (2020) 70 EP123 | DOI: 10.1530/endoabs.70.EP123

John Berquist, Jason Kaplan & Tessa Young. Euglycemic DKA after initiating an SGLT-2 Inhibitor and the P90X diet. Endocrine Abstracts (2020) 70 AEP320 | DOI: 10.1530/endoabs.70.AEP320

Jason G. Kaplan MD, Jay Mohan DO, Arjun Kanwal MD, John Berquist DO, Victor Hunyadi DO, John Q. Dickey DO, Melissa Marie Ianetelli DO. A Rare Case of a Undiagnosed Anomalous Right Coronary Artery from Pulmonary Artery after an Elective Esophagogastroduodenoscopy

Presentation at European Society of Cardiology Congress 2020- 8/31/2020. Presentation at Amsterdam, Netherlands originally- conducted virtually

Jason G. Kaplan MD, Arjun Kanwal MD, Adam Bykowski DO, John Berquist DO, Andrew Mirocke MD, John Q. Dickey DO. Hypertensive Emergency Presenting with Intraventricular Hemorrhage. Presentation at the American Heart Association Hypertension Scientific Sessions 9/2020. Presentation in New Orleans, LA originally-conducted virtually

Zane, Maamoun MD; Salih,Riyadh MD; Alkhankan, Fadi MD. Rare presentation of collapsing focal segmental glomerulosclerosis with acute interstitial nephritis secondary to Plasmodium Falciparum infection. MOA Autumn Virtual CME Program November 7-8/ 2020

Zane, Maamoun MD; Salih,Riyadh MD; Alkhankan, Fadi MD. Delayed hemolytic transfusion reaction (DHTR) due to JKB antibodies presented with association of acute kidney injury that required renal replacement therapy. MOA Autumn Virtual CME Program November 7-8/ 2020

Zane, Maamoun MD; Salih,Riyadh MD; Saiyed,Azim,DO; Alkhankan, Fadi MD . Mycoplasma Pneumoniae-Induced Rash and Mucositis (MRIM); Challenging disease entity.MOA Autumn Virtual CME Program November 7-8/ 2020

J. Vollstaedt, M. T. Kashlan, A. Saiyed; Severe Trimethaprim Sulfamethaxole Induced Thrombocytopenia. Critical Care Case Reports: Toxicology and Poisonings Poster Session. Am J Respir Crit Care Med 2020;201:A1681

KARMANOS RECEIVES RENEWAL OF NCI CORE GRANT

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- Cancer Center members have conducted over 600 clinical trials and enrolled 6,596 patients on interventional trials and 2,797 on treatment trials. Currently, more than 150 investigational therapeutic agents are being studied in a variety of malignancies.
- The Food and Drug Administration (FDA) approved 72 new cancer-specific drugs. Through clinical trials, Karmanos has participated in the approval of 48 of these drugs.

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

ANNOUNCEMENTS AND WHAT'S NEW

Joan Morey

Karmanos Cancer Institute Clinical Trials Office is pleased to introduce **Joan Morey**, Research Nurse. Joan is an experienced registered nurse with a Bachelor of Science in Nursing from Eastern Michigan University. Joan has been a Certified Clinical Research Coordinator (CCRC) since 2008 with primary research nurse experience in cardiovascular device and drug trials. We are excited Joan has joined our team and will be extending her strong research knowledge and support to the Karmanos Cancer Institute medical oncology and radiation oncology research program at McLaren Northern Michigan, Petoskey.

Amanda Snyder

McLaren Center for Research and Innovation is pleased to introduce our newest Clinical Research Coordinator, **Amanda Snyder**. She is a registered nurse with eight years of experience. Amanda began her career in radiation oncology before transitioning into oncology clinical trials with Karmanos Cancer Institute at McLaren Bay. By joining MCRI at the McLaren Bay site, she will primarily be working with cardiovascular and COVID-19 clinical trials. What Amanda loves most about clinical trials is the diversity of the role, as well as the patients she interacts with. We look forward to working with Amanda and watching her grow in her new role.

PROTOCOL DEVIATIONS VS. PROTOCOL VIOLATIONS

CONTINUED FROM PAGE 11

For example, study teams may want to periodically review their protocol with all research staff and check for and understanding. This might include checking that the correct version of the protocol is being used, carefully reviewing any amendments or modifications that have been made to the protocol, or beginning some form of internal monitoring as soon as enrollment begins.

Other ways to reduce deviations and violations include verifying that any eligibility criteria are clear and not subject to individual interpretation, taking time at the beginning of a study to predict possible protocol variances, and, prior to IRB submission, creating built-in contingency plans in the protocol.

Assuring that informed consent is obtained properly may also significantly reduce the incidence of deviations and violations. Make sure that study-specific procedures are performed after the informed consent has been signed, confirm that the informed consent discussion is conducted by an individual who is authorized to do so, and make sure that study subjects receive a copy of the signed informed consent form.

It is most important that everyone involved in a study know how to: (1) Identify protocol deviations and violations; (2) Report protocol deviations and violations; (3) Develop and implement a Corrective and Preventative Action Plan (CAPA Plan); and (4) Amend the protocol moving forward, if necessary.

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