

RESEARCH

FALL 2019

Matters



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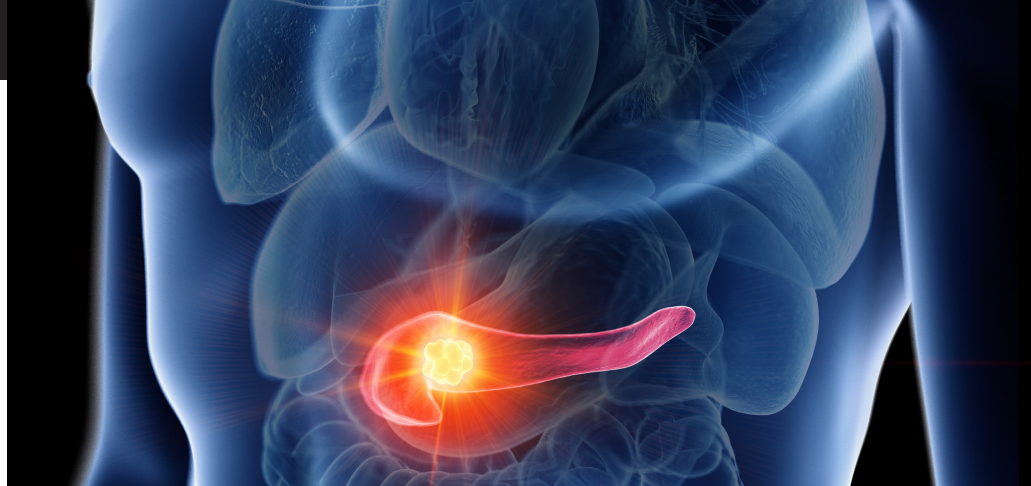
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RESEARCH AROUND McLAREN



A NOVEL THERAPY FOR PANCREATIC NEUROENDOCRINE TUMORS

Asfar S. Azmi, PhD, co-leader of the tumor biology and microenvironment program at Karmanos Cancer Institute, and assistant professor in the Department of Oncology at Wayne State University School of Medicine, has discovered how two proteins react to pancreatic cancer cells. The two

proteins, p21 activated kinase 4 (PAK4) and nicotinamide phosphoribosyltransferase (NAMPT), play a critical role in the development of pancreatic ductal adenocarcinoma and pancreatic neuroendocrine tumors.



Asfar Azmi, PhD

Dr. Azmi and his team have identified a drug that targets these two pancreatic cancer sustenance proteins. The drug has shown to be effective in blocking the growth of

pancreatic cell lines in patients' derived tumors.

Dr. Azmi's team has worked aggressively over the last several months to generate a considerable amount of scientific data using pancreatic neuroendocrine tumor models.

Pancreatic neuroendocrine tumors (pNET) account for approximately 7 percent of all pancreatic tumors. They develop from the abnormal growth of endocrine (hormone-producing) cells in the pancreas called islet cells. These cells play an important role in regulating the body's blood sugar levels.

"We have found two new therapeutic avenues for this difficult-to-treat disease," said Dr. Azmi.

"We have discovered that PAK4 and NAMPT are critical for pancreatic neuroendocrine tumor subsistence. Our team, working in collaboration with a pharmaceutical, has helped developed a new drug, KPT-9274, that works as a PAK4-NAMPT dual inhibitor. Our studies show that by blocking PAK4-NAMPT using biological means or through KPT-9274, we can suppress the proliferation of pancreatic

neuroendocrine tumor cell lines. We are also able to demonstrate the anti-tumor activity in animal models of pancreatic neuroendocrine tumors."

The data Dr. Azmi and his team were able to obtain from their research was reported in Abstract 4368: PAK4-NAMPT Dual Inhibition as a Feasible Strategy for Treatment of Resistant Pancreatic Neuroendocrine Tumors. The paper was shared at the American Association for Cancer Research 2018 Annual Meeting.

Thanks to seed funding from the Sky Foundation Inc. and Karmanos' Partners Night 2018, Dr. Azmi's team was able to perform a series of critical experiments that moved his project forward. The data obtained from these experiments was a significant element to support earlier findings. As a result, Dr. Azmi submitted a grant application to the National Institute of Health/National Cancer Institute for additional funding for this work. The grant is currently under review and the results are expected in late 2019.

Dr. Azmi added, "These efforts strengthen the case for the use of the drug KPT-9274 for the treatment of pancreatic neuroendocrine tumors."

Along with this scientific progress, Dr. Azmi's lab is in the planning stages to initiate a Phase I clinical study testing the safety and efficacy of KPT-9274 in patients with pancreatic neuroendocrine tumors.

Dr. Azmi's team who helped develop this research include Gabriel Mpilla, Amro Aboukameel, Irfana Muqbil, Steve Kim, Rafic Beydoun, Philip A. Philip, Ramzi M. Mohammad, Mandana Kamgar, Vinod Shidham, William Senapedis, Erkan Baloglu, Jing Li, Gregory Dyson, Yue Xue and Bassel El-Rayes.

"Dedicated team collaboration and funding are both critical for the advancement of cancer research that can lead to innovative treatments and better outcomes for those faced with this challenging disease."

THE INS AND OUTS OF FEASIBILITY REVIEW

By Pam Wills-Mertz

Examining the feasibility of a research study is essential to its ultimate success. Feasibility review evaluates studies involving human subjects regarding operational and financial impact. The principal investigator (PI) must ensure they have the time, staff, funding, and other resources to successfully conduct the study. The McLaren Center for Research and Innovation assesses feasibility by committee review. The Feasibility Review Committee (FRC) is a multi-disciplinary group designed to assist researchers in answering the questions often posed regarding their proposed study. The FRC is chaired by interventional cardiologist, Mark Zainea, MD, FACC, FSCAI from McLaren Macomb. He is an experienced research clinician and a strong advocate of clinical trials. The FRC members include representatives from pharmacy, supply chain, cath lab and finance, as well as the research team and other service line representatives.

The feasibility review process as led by Dr. Zainea poses many questions that must be addressed in order to determine whether the study should be accepted and moved forward for a scientific review. One question is that of time. Does the PI have adequate time to devote to the study and will the study be open long enough to enroll the appropriate number of patients? The workload of the research coordinator is also assessed for time and effort requirements. New studies should not jeopardize ongoing research.

Availability of resources is a common feasibility discussion as we bring on more and more studies that involve multiple disciplines such as laboratory, respiratory therapy or nursing. Conversations about coordination of efforts and study logistics must be had prior to feasibility review. Resource evaluation also includes reviews of equipment or devices required for the study.

Another area that is evaluated in the comprehensive review of feasibility is the study population. Does the site have the correct population to enroll in the proposed study? Is it reasonable to expect that enough patients will agree to participate and complete the study during the planned time frame? MCRI enters into legal contracts with clinical trial sponsors that have an agreed upon enrollment target or number of patients, therefore it is essential to make sure the correct patient population is available to be screened and enrolled.

Finally, budgets and contracts must be reviewed for feasibility. Does MCRI agree to the terms set forth in the contract by the sponsor? Is there adequate funding to successfully manage the study? Budget and contract feasibility are additional methods of looking at resource utilization. While the PI's don't actively get involved in contract and budget negotiations, the MCRI staff is responsible to ensure these goals are met on behalf of the PI.

The feasibility review process can be seen by investigators as time-intensive and frustrating, but it is an essential step in ensuring a high likelihood of study success. Dr. Zainea wants potential investigators to understand "the FRC is not intended to block research. Our mission is to ensure coordination of resources is adequate



Mark Zainea, MD

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.

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RESEARCH AROUND McLAREN

ONCOLOGY RESEARCH PROJECTS

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 (bepler@karmanos.org) and Dr. Lawrence Flaherty (flaherty@karmanos.org) if you are interested in activating an oncology related clinical trial or research project.

CONGRATULATIONS McLAREN NORTHERN RESEARCH TEAM!

The MCRI Team at McLaren Northern had an amazing 3rd quarter. They more than doubled their patient enrollments from the prior six-month period and accomplished this in only three months.

The Northern research staff consists of four coordinators: registered nurses Denise Antonishen, Mary Catton, Colleen Shaw, and Peggy Ward. This team is supported by research assistant, Lisa Rogers.

When asked what they attributed this dynamic quarter to, they report numerous factors. One recent change was a modification to a study that allowed for an additional population of patients to be enrolled. Additionally, three new clinical trials were opened. These trials were some of the first to go

through the MCRI Feasibility Review Committee and have been found to be successful to patient enrollment.

Aside from study openings and modifications is the time and effort of the research staff. Currently at McLaren Northern the research staff screens 12 patients to each one that is enrolled. Their efforts to advance medical science, as well as improving the health and well-being of our patients, shows dedication to research.

McLaren patients involved in clinical trials are often provided choices for their care beyond the standard available treatment. These treatments would not be possible with the efforts of the clinical research staff. Thank you to the Northern team!

KARMANOS PRESENTS AT AACI CLINICAL RESEARCH MEETING

The Karmanos Cancer Institute Clinical Trials Office had the honor of presenting three posters at the 11th Annual Association of American Cancer Institute Clinical Research Innovation Meeting, July 9 – 11, 2019 in Chicago, Illinois. The posters, featured in the 'Clinical Research Operations' and 'Trial Start-up/Closure' categories, received great feedback with many attendees mentioning it was great to see employees working in groups, taking initiative and leading employees in workplace engagement and satisfaction. For additional information, please call 313-576-9790.

Clinical Trials Office New Study Committee: A Streamlined and Collaborative Approach for Clinical Trial Portfolio Management

Sarah Bigelow, CCRP; Kasha Krul, CCRP; Maureen Kelley, MSBMS, CCRP; Lisa M. Lange, MSN, ANP-BC, AOCN

Multifunctional Staff Focus Groups as a Tool to Improve Employee Engagement of Clinical Trials Office Staff

L. Lange, AOCN, ANP BC; S. Bigelow, CCRP; C. Brown, CCRP; P. Dykema, CCRP; D. Erickson, CCRP; L. Jakovski

The Elephant in the Room –Onboarding of New Staff in an Evolving Research Landscape Plagued by Turnover

Dina Farhat BS, MS; Jaclyn Ventimiglia BS, CCRP; Elizabeth Horvat BA, MEd, CCRP; Lindsay Casetta BSBA, CCRP; Joanne Mancini RN, CCRP





*Andrew Jablonowski, ANP-BC,
and Maggie Perry, ANP-PC.*

NURSE PRACTITIONERS' RESEARCH INVOLVEMENT ON THE RISE

Research is a team effort and involves a multi-disciplinary team approach to be successful. Nurse practitioners are a vital part of the research process to ensure patient experience with research is positive and streamlined with their clinical care.

McLaren Macomb cardiac nurse practitioner Andrew Jablonowski has just begun his career journey in research. Along with fellow cardiac nurse practitioners, Alissa Clyne and Maggie Perry, he participated in training courses to begin this endeavor.

"We are really just beginning research in general as cardiac nurse practitioners at McLaren Macomb, so everything is fairly new," said Andrew. "Alissa, Maggie, and I took research courses to begin our training. We learned how to read the research and utilize it effectively, how to run simple research projects and get a feeling for how they operate, and how to do statistical analysis."

"Right now, the three of us have started by working on smaller trials as sub-investigators in cardiology research studies," he said. "We are starting with very basic roles and will work our way up as we gain more experience. As sub-investigators, we work with the PI, as well as with cardiac fellows and other

physicians. There are two main clinical research trials we are currently working on. They are the Connect HF study and the Deliver study." Both studies are in regard to heart failure.

"Our role in these two studies is to identify specific patient candidates based on set criteria that the patient's condition meets," he said. "First off, the patient must be an inpatient and have an acute illness. We review the patient chart to see if they meet the requirements for the study, and, if they do, we ask if they have any interest in participating in the study. If they are interested, we pass the patient's information onto the clinical research team, and the study coordinator

discusses participation with them. If the participation is agreed upon with the patient, then they are enrolled in the study."

According to the McLaren Center for Research and Innovation, the involvement of nurse practitioners in these studies helps to keep the lines of communication open, promoting a strong working team, comprised of many members. This not only increases the success of clinical trials, but the success of how well patients are cared for.

Although nurse practitioners are fairly new to the research at McLaren, they are gaining momentum in the field. "The idea now is for us to find our way and place throughout these clinical trials as they are still very new for us," said Andrew. "For now, we remain sub-investigators, but there may be avenues in the future in which we will look to present our own studies and become principal investigators ourselves."

THE INS AND OUTS OF FEASIBILITY REVIEW

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for study success. The study must be feasible for good research to occur." A recent potential study was stalled at the FRC level due to multiple questions regarding the resources and logistics of the study. The PI, sub-investigators, research staff and Dr. Zainea met to discuss the study. The team was able to smooth out the obstacles and the

study was then found to be feasible. He further states, "good research should never be easy. When human subjects are involved, there is no room for error in research decision making."

RESEARCH AROUND McLAREN

DR. STEPHAN PATRICK 2019 KALES AWARD WINNER

Stephan Patrick, PhD, has focused his research on studying how cancer cells respond to chemotherapy to improve treatment options for patients.

Dr. Patrick began his PhD program in 1994 where he noted, “I was drawn to platinum-based drugs in trying to understand how they function and determine how cancer cells become resistant to therapy.”

Dr. Patrick, associate professor in the Department of Oncology and member of the Molecular Therapeutics Program at the Barbara Ann Karmanos Cancer Institute since 2014, and Wayne State University School of Medicine, has

“ I WAS DRAWN TO PLATINUM-BASED DRUGS IN TRYING TO UNDERSTAND HOW THEY FUNCTION AND DETERMINE HOW CANCER CELLS BECOME RESISTANT TO THERAPY. ”

— Stephan Patrick, PhD

been selected as the 2019 winner of the Anthony and Joyce Danielski Kales Endowed Faculty Award for Innovative Cancer Researcher.

The Kales Award was created in 2012 at WSU SOM to recognize exemplary and innovative cancer research. It is supported by the Drs. Anthony and

Joyce Danielski Kales Endowed Faculty Award for Innovative Cancer Research Endowment. Selection is based on a comprehensive review of published articles within the previous year.

Dr. Patrick will be honored at Karmanos' Grand Rounds ceremony on October 24th in the Hudson Webber Cancer Research Center's Wertz Auditorium, in Detroit. He will speak about his research, specifically the publication for which he is being recognized, “Identification and Characterization of Synthetic Viability with ERCC1 Deficiency in Response to Interstrand Crosslinks in Lung Cancer.”

His article was published in the *Clinical Cancer Research* in 2018.

The research was executed by a team from the Molecular Therapeutics Program and Biostatistics Core at Karmanos Cancer Institute and Wayne State University. His co-authors include WSU graduate students, Joshua R. Heyza, PhD, and Donovan Watza, PhD; research technicians, Hao Zhang and Wen Lei; and faculty colleagues, Wei Chen, PhD; Jessica B. Back, PhD; Ann G. Schwartz, PhD, MPH; and Gerold Bepler, M.D., PhD.

Dr. Patrick and his colleagues identified a combative way to exploit cancer-specific loss of ERCC1, a DNA endonuclease that plays a critical role in mediating platinum-based chemotherapy response. Many cancer treatments, especially in lung cancer, include a platinum-based regimen, and so it is important to identify biomarkers of platinum-based chemotherapy response. Loss of ERCC1 and its utilization as a biomarker for platinum



Stephan Patrick, PhD

response in lung cancers has been investigated previously by numerous researchers, however, there has been controversy and lack of clinical value to date. Importantly, in the study conducted by Dr. Patrick and colleagues, they uncovered the importance of the p53 gene in mediating sensitivity to platinum-based chemotherapy in response to this ERCC1 deficiency. Also known as the “tumor suppressor protein,” p53 helps control apoptosis and mediates cell-cycle control; however, the loss of p53 uncovers an alternative, error-prone pathway that enables cells to tolerate platinum-based chemotherapy with ERCC1 loss. Together, the team was able to identify a synthetic viable phenotype in ERCC1-deficient cells when p53 is mutated. Of utmost importance, the team was able to identify novel drug combinations that would overcome the drug tolerance in the lung cancer cell line models and restore a hypersensitive phenotype.

Collaborating with Dr. Bepler, president and CEO of Karmanos Cancer Institute, since the beginning of his career at Karmanos, Dr. Patrick and his team are avidly working to initiate clinical trials, starting with lung cancer and expanding to other cancers from the research conducted. In addition, they are working to publish a follow-up paper to announce a new drug combination to treat platinum-tolerant cancer cells that result in hypersensitization to platinum-based chemotherapy.

Dr. Patrick noted that understanding the molecular mechanisms of resistance to DNA crosslinking agents can be linked

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NEW ACADEMIC YEAR; NEW FORMS, UPDATES, AND FORMATS

McLaren's Division of Scholarly Inquiry (DSI) would like to join the McLaren Health System in welcoming new and returning residents/fellows/faculty. The new academic year 2019-2020 will bring new ideas and scholarly projects that will contribute to vertically advance health care knowledge and practice. The DSI is always adapting and updating its processes to meet the challenges and demands of promoting, facilitating, supporting, and encouraging scholarly activity across five hospitals and over 500 residents/fellows/faculty. The DSI is committed to receive and evaluate the comments, suggestions, and recommendations of all McLaren staff participating in graduate medical education. As a result of this commitment and in appreciation to all of those that provided their feedback, the DSI has developed new forms, eliminated some, and updated others for the academic year 2019-2020.

A new Scholarly Activity Review Committee application form has been developed that is shorter, simpler, and with more and clearer instructions. This new form will replace the previous one that many residents/fellows/faculty found long, difficult, and cumbersome to complete. In collaboration with the Institutional Review Board, the Determination of Human Subjects Research and the Scientific and Scholarly Validity forms have been updated with better instructions, improve layout, and now include a PhD signature area as a reminder that these forms need to be signed by the PhD prior to emailing them to the IRB. Another update was the addition of hyperlinks to the Scholarly Activity Stages' flowchart where ever a form was mentioned in the figure. This flowchart now also includes the Protocol Review Committee requirement for prospective and interventional studies. Last but

not least, the DSI has developed its very own webpage for PhDs to have a one stop place where they can find everything related to scholarly activity. It is expected that after a period of three months and with the feedback of PhDs, residents/fellows/faculty will have their own Scholarly Inquiry webpage to access everything related to scholarly activity on their own.

The DSI is also pleased to announce the development of a new journal club (JC) format and its successful piloting across residency programs in McLaren Oakland. This new JC format will be implemented system wide during academic year 2019-2020. Similarly, the DSI developed a new teaching and training curriculum content and sequence focusing on research methods, statistics, and other aspects related to scholarly activity (i.e., electronic searches of the medical literature, IRB/ethical requirements, dissemination of scholarly activity, etc.) for residents/fellows using a flipped classroom format that will also be implemented across the McLaren system during academic year 2019-2020. Initial feedback from residents/fellows/faculty shows very good acceptance and relevance. Finally, the DSI has developed an authorship policy in an effort to clarify, standardized, and prevent conflicts.

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 faculty. For additional information contact Dr. Carlos F. Ríos-Bedoya at carlos.rios@mclaren.org

FACULTY, FELLOWS & RESIDENTS SCHOLARLY ACTIVITY NEWS



Carlos F. Ríos-Bedoya, ScD

FACULTY, FELLOWS & RESIDENTS SCHOLARLY ACTIVITY NEWS

(Left to right) Drs. Carlos F. Ríos-Bedoya (Corporate Director of Scholarly Inquiry, McLaren Health Care), Ghareebian Hagop (Co-author of 1st Place Resident Poster, McLaren Flint), and Robert F. Flora (Chief Academic Officer & Vice President of Academic Affairs, McLaren Health Care) at the 4th Annual Michigan Summit on Quality Improvement, Patient Safety, & Wellness (2019), Troy, MI.



2018-19 RESIDENTS PROJECT AWARDS



McLaren Flint

- **Implementation of a COPD Management Plan to Improve Compliance with Evidence-based Guidelines**

Ali Ahmad, MD, Ghareebian Hagop, MD, Tryphene Saint-Phard, MD, Lakshmi Kolly, MD, Orimisan S. Adekolujo, MD

Won 1st Place for Resident Poster at the 4th Annual Michigan Summit on Quality Improvement, Patient Safety, & Wellness (2019), Troy, MI

- **The Return on Investment of Orthopaedic Fellowship Training: A Ten-Year Update**

Matthew Mead, DO, Theresa Atkinson, PhD, Ajay Srivastava, MD, Norman Walter, MD

Won Best Resident Paper at the 2019 Michigan Orthopaedic Society Annual Scientific Meeting, Traverse City, MI

- **No One Should Be Afraid of the Water – Somatic Symptom Disorder and Illness Anxiety Disorder in the Aftermath of the Flint Water Crisis**

Syed Zaidi MD, Erin O'Connor PhD, Megha Garg BS, Prabhat Pokhrel MD, PhD, Barbara Wolf PhD

Won First Place for Resident Research at the American Academy of Family Physician's Family Medicine Experience, New Orleans, 2018



McLaren Greater Lansing

- **Identification of Risk Factors for Surgical Site Infections after Cesarean Section at a Small Community Hospital: A Retrospective Chart Review**

Emily Henning, DO (MGL OBGYN-PGY4) – Now graduated and Robert Seiler DO, FACOOG

Won 2nd Place Poster Presentation at the 2019 SCS George W. Russian Memorial Research Day

- **Novel Technique to Assess Glenoid Bone Loss Compared to True Fit Circle Technique Using Magnetic Resonance Imaging**

Stanley D. Crawford, DO (MGL Ortho-PGY5) – Now graduated, Christopher L Wilcox, DO, Neil Olmscheid, DO, Ryan Fajardo, MD, Patrick Joyner, MD, Jeffrey Knake, M.D., Christopher Dickinson, DO

Won 2nd Place Oral Presentation at the 2019 SCS Orthopedic Surgery Research Day



McLaren Macomb

■ Isolated Pleural Nocardiosis in Immunocompetent Male

Anila Rao, DO, Edward Chi, DO, Kathleen Jahoda, PA-C, Dheeraj Thammineni, MD, Anthony Ognjan, DO

Won Case Report Presentation Prize Presented at Michigan Osteopathic Association (MOA) Seventh Annual Autumn Scientific Convention

■ A Rare Case of a “Broken Heart” Causing Papillary Muscle Rupture

Anila Rao, DO, Vasim Lala, DO, Don Tait, DO, Vivek Sengupta, DO, M. Blair DeYoung, DO

Won 1st place for Case Report Presentation at Michigan Osteopathic Association (MOA) 120th Annual Spring Scientific Convention



Anila Rao, DO



McLaren Oakland

■ Comparison of associated comorbid conditions in patients with benign paroxysmal positional vertigo with or without migraine history: a large single institution study

Daniel B. Hilton, DO, Alexander L. Luryi, MD, Dennis I. Bojrab, MD, Seilish Babu, MD, Robert S. Hong, MD, John Zappia, MD, Eric W. Sargent, MD, Olga J. Santiago Rivera, PhD, Christopher A. Schutt, MD

Won 2nd Place Oral presentation at MSU-SCS 4th Year ENT Research Symposium, April 2019, Novi, MI

■ Single-Center Retrospective Analysis Evaluating the Safety and Efficacy of a Pharmacist vs Physician-Managed Inpatient Warfarin Dosing Service

Jason G. Kaplan, MD, Usama Ashraf, PharmD, M. Zeeshan Rizwan, PharmD, Vasim Lala, DO

Won 3rd place in clinical vignettes at the MSUSCS Research Poster Competition, May 2019, East Lansing, MI

We sincerely regret if we left out any resident, but we had a publication deadline and had some challenges gathering the information from all residency programs. 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.

2019 KALES AWARD WINNER

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to improving patient responses to platinum-based chemotherapy.

“Targeting DNA repair pathways to enhance platinum-based chemotherapy will make a significant contribution to the treatment of cancers.”

Reflecting on his future research, Dr. Patrick mentioned that researchers are “trying to devise new treatment options for the 10 to 15 percent of non-small cell lung cancers (NSCLC) that are ERCC1 deficient and p53 mutated, and which do not typically respond well to platinum-based chemotherapy.” Furthermore, he noted that adding another drug to the regimen of this population of NSCLC would potentially enhance the effect of platinum-based drugs, which will remain as part of the standard of care. His research significantly influences the chemotherapy options for not just lung cancer exclusively, but for many cancers with low ERCC1, most commonly seen in ovarian cancer.

Dr. Patrick added, “To achieve the best response, exploiting the DNA repair deficiencies in cancer cells and targeting them with specific chemotherapeutic drugs is critical to the future of platinum-based therapy.”

Dr. Patrick will be recognized as the 2019 Kales Award recipient. He commented, “I’m shocked, but at the same time I am deeply honored.”

EQUIP CORNER

USING A NOTE-TO-FILE IN CLINICAL RESEARCH

By Marybeth McCarthy

Using a “note-to-file” (NTF) to relay information in research records is a very common practice. In my personal audit experience, I have noticed an increase in the use of NTFs. This has also been reported in research literature. What is the root cause of this increase? Is it due to overuse or abuse? Or perhaps just a shift in procedures. In order to answer these questions, we will take a closer look at the purpose of the NTF, regulations as they apply to the use of the NTF, and the appropriate use of the NTF.

What is a NTF?

A note-to file, also referred to as “memo to file” (MTF), is a document used to explain or clarify a situation or add information to a file during the conduct of a research trial. For example, a NTF may document a corrective action, provide missing information, explain an action or mistake, provide clarification regarding a discrepancy.

What do the regulations and good clinical practice guidelines say about NTFs?

Health and Human Services research regulations and ICH guidelines on good clinical practice (GCP) contain no specific guidance on the use of NTFs. The Code of Federal Regulations does, however, state that the investigator is responsible to maintain adequate, complete and current research records [21 CFR 312.62 and 21 CFR 812.140(a)].

The ICH GCP (adopted by FDA as guidance) standard on documentation

states that all clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. Furthermore, any discrepancies in the data collected should be explained. In essence, regulations and ICH GCP don't directly address the term NTF, although there is an expectation that information will be adequately captured throughout the conduct of a study.

When is it appropriate to use a NTF?

The following are examples of how a NTF can be used to clarify, explain or add information:

- Noting location of a document, if it is not filed in its designated location (i.e. the delegation log)
- Explaining a situation occurring with a specific subject that led to a deviation. For example:
 - A subject did not take study medication as directed and failed to document this in the drug diary because they did not understand the directions given to them. A NTF can be used to indicate that additional instruction will be given to the subject using the teach back method. In this example the NTF both identified the problem is identified and provides a solution.
 - A subject was consented with the incorrect version of the consent and it is determined the obsolete version had not been removed from the file. A CAPA plan is initiated to re-consent the

patient with the correct version at the next visit and destroy any remaining unused forms. In addition, other subject files will be reviewed to ensure the correct version has been used. A NTF can be generated explaining the circumstances as well as the details of the CAPA plan.

The key to proper use of a NTF is ensuring that the information is provided in such a manner that future auditor, monitor or regulatory inspector will understand the specifics of a situation and, if necessary, the solution.

When is it not appropriate to use a NTF?

A NTF should not duplicate or replace information that should be written in a subject's research record. In other words, a NTF should not be written without an effort to determine if the documentation has been completed and can be in the subject's source document, the monitoring report, in e-mail correspondence, etc.

Additionally, a NTF should not compensate for lack of PI oversight or documentation, such as protocol eligibility criteria.

Remember, a NTF should not be used to coverup the underlying problem. For example, using a NTF to document repeated deviations does not negate the fact that deviations have occurred, nor is it a solution to the problem. A NTF will only magnify the fact that documentation is incomplete, and/or that the protocol is not being followed in this example. The following are some

instances of the misuse of NTFs, as noted by Food and Drug Administration inspectors in the warning letters:

taken and the subsequent results of this action. Identification of a problem, including root cause analysis, and

An FDA Warning Letter dated October 23, 2007 states: "Our investigation found (the sponsor) failed to take any action except to generate numerous memos to file after all the subjects completed the study."

www.fda.gov/foi/warning_letters/s6551c.htm

An FDA warning letter issued to Sanofi Aventis in October 2007 states: "Serious non-compliance was found in the informed consent process. NTF's were written to resolve this issue." The inspector states in the warning letter, "memos to file are inadequate to address the falsification (backdating) of study documents".

www.fda.gov/ICECI/EnforcementActions/WarningLetters/2007/lucm076552.htm

These examples clearly demonstrate that a NTF cannot replace proper documentation and procedures, and therefore cannot be used to resolve a problem. An appropriate solution to issues arising at a site must explore the root cause of a problem and provide steps to ensure they are not repeated.

How should a NTF be created?

An adequate NTF should clearly stand out as a note-to-file and should:

- Be written on institution letterhead
- Contain the date, IRB number, study title, sponsor name
- Identify to whom the NTF is addressed
- Identify who the NTF is from
- Contain a topic and a content section. (The content section should include a description of the problem including specific subject identifier or staff, root cause, the changes need, the changes implemented and resolution of the problem.
- Be reviewed and signed by the principal investigator.

In summary, a NTF can be effective if well written, relevant, timely and infrequent. Too many NTF's tend to magnify poor performance and create red flags in audit situations.

Documenting a problem means nothing by itself. An auditor is looking to see if corrective action has been

implementing corrective action that leads to resolution assures sponsors and regulators that you are serious and proactive in ensuring subject safety and data integrity.

Don't let the habit of writing NTFs overshadow the need to develop good record keeping practices. If you need any assistance with writing a note-to-file or a template call the Office of Research Compliance and QI at (248) 484-4987.

BROWN BAG SERIES

UPIRSO's

What Do I Need to Know?

September 10, 2019 12:00-12:45
LIVE WEBINAR

HUD/HDE's: An Overview

December 10, 2019 12:00-12:45
LIVE WEBINAR

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

UPCOMING RESEARCH EDUCATION

SOCRA 28th Annual Conference

San Antonio, TX
September 27-29, 2019

MAGI Clinical Research Conference – 2019 West

Las Vegas, NV
October 27-30, 2019

ACRP 2020

Seattle, WA
May 1-4, 2020

2020 AAHRPP

Annual Conference
Baltimore, MD
May 19-21, 2020

ANNOUNCEMENTS AND WHAT'S NEW



Emily Thompson, BSW
Clinical Research Assistant
MCRI – Macomb
Emily comes to us eager to learn research and utilize her clinical background as an EMT. Emily has a bachelor's degree in Social Work from Oakland University and a great deal of administrative experience. Emily provides administrative support to our research office at McLaren Macomb and hopes to advance her career in research with McLaren.

Emily Thompson

research office at McLaren Macomb and hopes to advance her career in research with McLaren.



Breeanna O'Lear, BBA
Clinical Research Assistant
MCRI – Flint
Breeanna previously worked at McLaren Lapeer as staffing clerk for nursing. She has a bachelor's degree in business administration from Baker College and brings experience in critical thinking, as well as improvement to MCRI.

Breeanna O'Lear

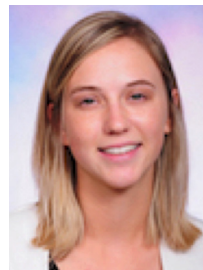
Breeanna provides administrative support to our research office at McLaren Flint and is excited to learn research while discovering how to apply her knowledge to better our current processes.



Laurie Nightengale, MD
Clinical Research Coordinator
MCRI – Greater Lansing
Laurie is an experience research coordinator who recently graduated from medical school. She has her MD from All Saints University School of Medicine and plans to use her medical degree to advance her research

Laurie Nightengale

career. Laurie has a strong background in non-oncology research and looks forward to expanding her skill set with our cardiology investigators at McLaren Greater Lansing.



Sydney L. Whitson, BS
Clinical Research Coordinator II
Karmanos Cancer Institute at McLaren Greater Lansing
Congratulations to Sydney for her recent promotion to Clinical Research Coordinator II.

Sydney Whitson

THE KCI CLINICAL TRIALS OFFICE REGULATORY TEAM IS GOING ELECTRONIC!

- Research personnel will be able to view and sign clinical trial regulatory documents electronically via the eREG™ system
- eREG™ training is required through Forte Academy in order to use the system & to participate on KCI clinical trials managed by the CTO. All personnel will receive an e-mail invitation from Forte Academy to join the Forte Academy learning portal via a link. Once your profile

is created, you can then begin completing all required courses for your role. If you are enrolled in additional courses, you will receive a notification email with a link to access the course. All Forte Academy training certificates must be sent to ctoereg@karmanos.org.

- If you have not received a training email or if you have questions regarding eREG™ or Forte Academy, please email ctoereg@karmanos.org

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