RESEARCH *Matters*

SUMMER 2018

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

McLaren | DOING WHAT'S BEST.

McLaren RESEARCH Matters

(L-R) Leading Karmanos Cancer Institute's CAR-T therapy are **Abhinav Deol, MD**, medical oncologist at Karmanos and associate professor, Wayne State University School of Medicine; and **Joseph Uberti, MD, PhD**, Karmanos division chief of Hematology and co-director of Bone Marrow Transplant, and professor at Wayne State University School of Medicine.

KARMANOS' COMMITMENT TO RESEARCH LEADS TO REVOLUTIONARY CANCER TREATMENT

By Abhinav Deol, MD and Joseph Uberti, MD, PhD

In 2018, Karmanos Cancer Institute became the first center in Michigan approved to treat adult patients with diffuse large B-cell non-Hodgkin lymphoma with the commercially approved chimeric antigen receptor (CAR) T-cell therapy. Karmanos Cancer Institute took part in the CAR-T clinical trials that led to the U.S. Food and Drug Administration (FDA) approval of CAR-T therapy for this type of lymphoma in October 2017.

Dr. Joseph Uberti, MD, PhD, Karmanos division chief of Hematology and co-director, Bone Marrow Transplant, and professor, Wayne State University School of Medicine, discusses how a decades long commitment to research lead to this groundbreaking therapy.

Karmanos was approached by one of the pharmaceutical companies that was running investigational protocols for CAR-T cells. The company was looking for centers with large stem cell transplantation programs that had experience in administering cellular immunotherapy. They approached one of our clinical investigators, Dr. Abhinov Deol, about participating in one of the early Phase II investigational trials.

Karmanos was chosen to conduct these clinical trials due to a number of advantageous factors. Our center had developed expertise in stem cell transplantation with experience doing clinical trials. The handling, development and safe administration of CAR-T cells requires the infrastructure of a large transplantation program. Our program had experience in cellular preparation, cryopreservation, administration, and care of patients undergoing various forms of cellular therapy. We also have the presence of a large experienced clinical trials staff that could meet the regulatory and data management issues of these complex clinical trials. All the requirements to administer and evaluate CAR-T cells are built into our stem cell transplantation programs, making Karmanos ideal for these clinical trials. In addition, we developed a multi-disciplinary team required to care for these patients which includes our ICU, infectious disease and neurology services. There are some unique toxicities involved in the administration of these cells, which makes the involvement of a large multi-disciplinary team critical.

WHY RESEARCH MATTERS

The response to our clinical trials for CAR-T therapy has been exceptional. Approximately 80% of patients have shown some response, with 40% achieving a complete remission. Some of these complete remissions have lasted several years and the hope is they will prove to be curative.

Karmanos has shown a commitment to research as we have successfully participated in many complex clinical trials. This commitment to our research mission has made us an attractive partner for pharmaceutical companies to collaborate with. These partnerships have allowed us to bring innovative therapies such as CAR-T cell therapy to our center, resulting in much success for our patients.

McLAREN MEETS KEY GOAL WITH ACCEPTANCE INTO NIH STROKENET

By Aniel Majjhoo, MD

WHY RESEARCH MATTERS

A key goal for the McLaren Neuroscience Research Council was achieved in April with McLaren's acceptance into the NIH StrokeNet program. In order to be accepted into NIH StrokeNet, applicants must hold Comprehensive Stroke Center certification and meet specific quality and outcomes criteria.

Funded by NIH, StrokeNet's primary goal is to maximize efficiencies to develop, promote and conduct high quality multi-site clinical trials focused on key initiatives in stroke prevention, treatment, and recovery.

The StrokeNet infrastructure consists of 25 regional coordinating centers across the United States, a national coordinating center at the University of Cincinnati and a national data management center at the Medical Universiy of South Carolina. McLaren is part of the University of Michigan regional coordinating center.

"As part of the NIH StrokeNet initiative, we can now participate in important national and international trials," said Dr. Aniel Majjhoo, chairman of the McLaren Neuroscience Research Council. "This gives us national recognition and represents another step forward in terms of our involvement in leading edge clinical trials."

Dr. Majjhoo serves as the Principal Investigator for McLaren Stroke Network clinical trials.

Aniel Majjhoo, MD
Neurology & Vascular Neurology
Board Certified
Interventional Neurology

RESEARCH GROWTH AT McLAREN

By M. Ammar Hatahet, MD, MPH, FACP

Over the years, we have seen a significant increase in the number of cardiology studies conducted at McLaren. This introduces more opportunities for patients to participate in trials. Cardiology studies have grown to be quite unique and are on the cutting edge of interventional cardiology.

We have also seen our principal investigators gain a much better understanding of federal regulations around research. This has aided in carrying out clinical studies in a more efficient and productive way.

Going forward, I anticipate an increase in the number of studies conducted at McLaren. My hope is to see not just cardiology studies, but other service lines such as interventional neurology and orthopedic studies. I also anticipate more sophisticated studies and designs from our principal investigators.

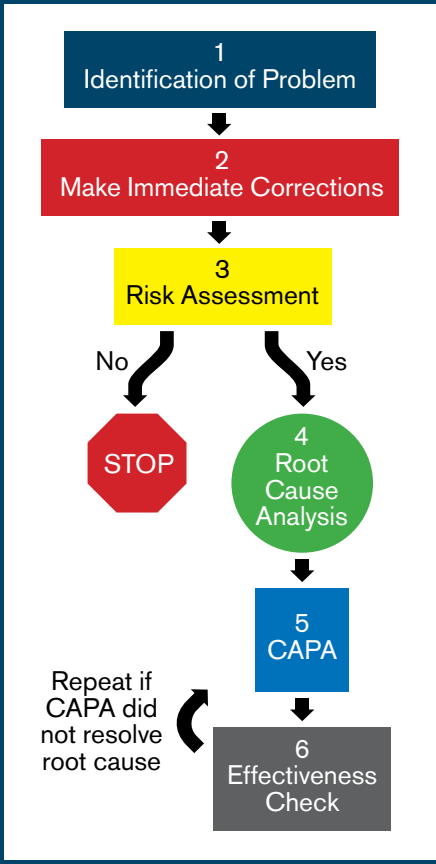
M. Ammar Hatahet, MD, MPH, FACP, is an internist and diabetologist in solo private practice. He was appointed as the Chairman of the McLaren Health Care Institutional Review Board (MHC IRB) in January 2012. Dr. Hatahet has been in clinical practice since 2004 where he continues to teach residents and students from Michigan State University.

M. Ammar Hatahet, MD, MPH, FACP
Internist and Diabetologist, and
Chairman of the McLaren Health Care
Institutional Review Board

EQuIP CORNER

Figure 1.

SYSTEMATIC APPROACH



MOVING FORWARD WHEN THE UNEXPECTED HAPPENS PART 1

Clinical research trials are becoming increasingly complex and highly technical. Even with the most cautious planning and meticulous actions, problems can occur. Regardless if the problem is a minor deviation or a major violation, it is important to ensure that:

- Issues are addressed promptly and properly, to prevent them from being repeated
- The scope of the impact of the deviation/violation is clearly understood and mitigated

All deviations/violations require some type of corrective action. In some cases, implementation of a formal corrective action preventative action plan (CAPA) may be necessary. A CAPA is a written plan that:

1. Clearly identifies the discrepancy or problem.
2. Notes the root cause of the identified problem.
3. Develops and implements the actions taken to both correct and prevent recurrence of the problem.
4. Evaluates whether the corrective measures have eliminated the problem.

When to Initiate a CAPA Plan

Determining if a CAPA is warranted requires a systematic evaluation of the deviation/violation (see figure 1).

Step 1 – Clearly define the problem. This requires looking at the problem source, conditions, location, occurrence times, number of subjects affected, personnel involvement, etc.

Step 2 – Quickly evaluate if immediate action is required to protect the rights, welfare, and safety of subjects(s), taking into consideration the reporting requirements of the sponsor and the IRB. (Detailed information regarding the reporting requirements of the MHC IRB can be found in McLaren policy MHC_RP0122) For example, if the incorrect study drug bottle is dispensed to a subject; or a subject is enrolled in an interventional study and later discovered to be ineligible.

Step 3 – Perform a risk assessment to determine the severity and scope of the problem. Start the risk assessment by looking at the information collected during Step 1 and ask the following questions:

1. Is the deviation human error or procedural error?
2. Where in the process did the problem occur?
3. When did the problem occur?
4. Who is responsible for the problem?
5. Did you have to notify the IRB and/or Sponsor?
6. How significant is the problem? In other words, what is the weight/ impact of the problem/ how severe is the problem? This can best be answered by:

a. Determining if the problem is minor or major non-compliance (Figure 2) and

b. Determining frequency of the problem: Assess the likelihood of the problem recurring in the same subject or other study subjects in the future; and review the protocol deviation log to assess past occurrences of the event. If there appears to be a pattern or risk of the problem recurring in the future, there is a risk of

frequency. Please note that when multiple minor non-compliance issues represent a trend, it may be a sign of potential major non-compliance.

Minor vs Major Non-Compliance
Minor non-compliance is neither serious nor continuing. It is defined as any behavior, action or omission in the conduct or oversight of research involving human participants that deviates from the approved research plan, federal regulations or institutional policies but, does or did not:

- Adversely affect subject's right, safety, and welfare
- Adversely affect the integrity of study data – Increase any harm or immediate hazard to subject
- Adversely affect subject's willingness to continue participation in the study

Serious Non-compliance:

- Creates an increase in risks to subjects, adversely affects the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study.
- May involve willful violation of policies and/or federal regulations may also constitute serious non-compliance.

Assessing the risk - If there is no risk of severity or frequency or the problem is minor (not critical and not significant) and there is a sufficient immediate solution, the non-compliance event can be closed with an effective containment or correction. Lastly, document on a note-to-file: the problem, risk assessment and corrections. Keep in mind that a note-to-file becomes part of the study record and provides a road map for any inspector. They should be kept few and far between. Numerous NTFs explaining the same problem may give the appearance of a systemic problem. In addition, continue to monitor the protocol deviation log for patterns.

A CAPA should be initiated if the problem:

- Is significant or critical
- Meets the definition of serious or continuing non-compliance
- Presents a risk of severity and/or frequency
- Is systemic minor non-compliance or process related

Step 4 – Before creating a CAPA, you must conduct a root cause analysis (RCA). Root cause analysis is the process of identifying underlying problems that contributed to the deviation. There can be multiple issues that contribute to one single problem. Identifying and eliminating the root cause should prevent recurrence of the problem.

Although there are a number of tools for determining root cause, we will focus on the "5 Whys" for the purposes of this article. The first step in using this tool is to state the identified issue. Writing down the specific problem is helpful to formalize and describe it completely. Ask "Why" the deviation happened, what behaviors occurred in the past and what actions were taken. Be sure to write the answer to each question. If the written answers do not identify the root cause of the issue, write each question again and document the response. Repeat these steps until the team is in agreement that the issue's root cause has been identified. This may take more than 5 attempts, or it may take less.

Step 5 – Once the root cause is defined you can develop appropriate corrective and preventative actions, which we will discuss in part 2 of this article in the next newsletter.

Figure 2.

MINOR VS MAJOR NON-COMPLIANCE

Minor non-compliance is neither serious nor continuing. It is defined as any behavior, action or omission in the conduct or oversight of research involving human participants that deviates from the approved research plan, federal regulations or institutional policies but, does or did not:

- **Adversely affect subject's right, safety, and welfare**
- **Adversely affect the integrity of study data – Increase any harm or immediate hazard to subject**
- **Adversely affect subject's willingness to continue participation in the study**

SERIOUS NON-COMPLIANCE:

- **Creates an increase in risks to subjects, adversely affects the rights, welfare and safety of the research subjects or adversely affects the scientific integrity of the study.**
- **May involve willful violation of policies and/or federal regulations may also constitute serious non-compliance.**

UPCOMING RESEARCH EDUCATION

SOCRA 27th Annual Conference
New Orleans, LA
Sept 28-30, 2018

MAGI Clinical Research
West Coast Conference
San Diego, CA
Oct 21-24, 2018

RESIDENT CORNER

Carlos F. Rios-Bedoya, ScD

PROTOCOL BUILDER FOR ALL INVESTIGATOR INITIATED STUDIES

As indicated in our last edition, Protocol Builder is now available to assist investigators in creating a protocol document. Use of Protocol Builder is not limited to residents and can be used by anyone wishing to create a protocol document for an investigator initiated study. For questions regarding Protocol Builder or to request access, please contact Dr. Carlos Rios-Bedoya, MPH, ScD, Corporate Director of Scholarly Inquiry at carlos.rios@mclaren.org.

RESIDENT RESEARCH SUBMISSION PROCESS EXPLAINED

By Carlos F. Rios-Bedoya, ScD

I have received some feedback regarding the scholarly activity process depicted in the Protocol Builder Read Me First document which was distributed in January. Subsequently, the process has been updated. In addition, it seems that some clarification is still necessary, particularly in regards to how to proceed after the brainstorming session. I will try to explain the thought process behind the updates, in hopes of facilitating the development of your research protocol.

After the brainstorming session with the PhD (and, hopefully, your faculty mentor), you should have a better idea regarding the likelihood that your project will be determined human subject research by the McLaren IRB. You might also want to consult one of the IRB analysts and clearly explain your project, providing as many details as possible. They may be able to provide additional assistance. Thereafter, you should start writing a draft of your research protocol using either Protocol Builder (if there is high likelihood that your project is human subject research) or the QI forms/templates found at https://sites.google.com/a/mclarenmeded.org/scholarly-activity/home (if there is high likelihood that your project is NOT human subject research). Concurrently, you should be working on completing the Request for Determination of Non-Human Subject Research and Confirmation of Scientific or Scholarly Review for Validity forms (found at: http://www.mclaren.org/main/research-irb-forms1.aspx). These forms, together with your research protocol document will need to be submitted to the IRB. Soon after the IRB receives the forms, they will determine whether or not your project is human subject research.

If your project is determined to be human subject research - you will complete your draft research protocol in Protocol Builder and complete an IRB application via the eProtocol electronic submission system. It is important to note that at this time Protocol Builder does NOT communicate or interact with eProtocol. This feature may be added in a future version of Protocol Builder. It is highly recommended that you contact an IRB analyst prior to accessing eProtocol, in order to determine what type of form is most appropriate (e.g., Chart review, exempt, or Full Board / Expedited) for your study. All supporting documentation for your study must be provided with your eProtocol application. This includes, but is not limited to, a MS Word version of the research protocol you created using Protocol Builder, data collection forms, flyers, consent forms, etc.

You will be notified if any clarifications/revisions to your eProtocol application and/or supporting documentation are necessary. Once the IRB is satisfied that they have adequate information to complete their review and make a determination, you will receive notice of their approval or disapproval of your project. In the event that your project is not approved, you must reapply to the IRB, beginning with a new eProtocol application.

If your research protocol is determined non-human subject research - you will submit the QI templates/forms to the Scholarly Activity Review Committee (SARC) for review and approval. The SARC will follow a similar approach to the communication and determination process as the IRB (described above).

IMPORTANT: You should NEVER begin your research project's data collection or abstraction or have contact with any patient/subject for research purposes without written approval of your research protocol from either the IRB or the SARC.

Hope this is helpful and good luck with your projects.

WHAT'S NEW?

CTMS UPDATE

McLaren Center for Research and Innovation is in the process of implementing a Clinical Trials Management System (CTMS) to support research operations across the system. The CTMS will be the source of truth for all study documentation, patient enrollment data, and research financials. Having all our study operations in a single system designed specifically for clinical research administration will allow us to streamline our current workflows significantly, leaving us more opportunity for the growth of our program.

MCRI at McLaren Greater Lansing is our pilot site and the rollout was successfully implemented on June 1, 2018. We will provide updates on the system implementation as more information becomes available.

COMMON RULE UPDATE

McLaren has been following the revised Common Rule activities. On April 19, 2018 a Notice of Proposed Rulemaking (NPRM) to delay the general compliance date of the Common Rule revisions by 6 months (from July 19, 2018 until January 21, 2019) was put on public display by the Office of the Federal Register. Comments on the NPRM must be received no later than 11:59 p.m. Eastern Standard Time on May 21, 2018. Keep an eye on the Research Integrity website (http://www.mclaren.org/main/research-hrpp.aspx) for more information. Updates will be posted as they become available.

NEW POLICIES AND PROCEDURES

The aim of the Corporate Research Administration is to enhance the platform on which we build our research program thereby providing improved structure and stability to support the growth of research at McLaren. The McLaren Center for Research and Innovation (MCRI) is currently revising and updating existing policies and procedures, as well as writing additional policies and procedures for the administrative office and the research sites.

The following are the new policies:

- MHC_CT0101_McLaren Center for Research and Innovation Oversight
- MHC_CT0102_Principal Investigator Responsibility and Oversight
- MHC_CT0103_Conflict of Interest in Research
- MHC_CT0104_Research Conducted at McLaren by Non-McLaren Investigator/Entities
- MHC_CT0105_CT0105_Feasibility Review Committee
- MHC_CT0107_Neuroscience Research Council

To obtain copies of these polices, please contact the Corporate MCRI office at (248) 484-4960

STAFF ANNOUNCEMENTS


Patricia Ivery

MCRI would like to welcome **Patricia Ivery,** RN, MSN as a new Corporate Research Manager for non-oncology research.

Patricia joined McLaren 5 years ago as a Quality Improvement and Education Specialist within the department of Research Integrity [formerly known as HRPP]. Patricia brings a wealth of knowledge and experience from all facets of research. She has a proven track record of success in the research field which will be invaluable in meeting the departmental goals and objectives.

Some of Patricia's responsibilities will include research informatics, management of IT projects across the system as well as facilitating non-oncology research and management of the research committees. Patricia will be working very closely with current Corporate Research Manager, Jill George, as we grow our non-oncology research portfolio.


Markeda Richards

We are pleased to announce the promotion of research team member **Markeda Richards** to the position of Research Administration Coordinator with the Corporate Research Administration Team.

Markeda has been a dedicated employee at McLaren since August 2015 and served in the role of HRPP Coordinator. During the restructuring of our research departments, Markeda has taken on additional responsibilities which have played a vital role during the transition.

In her new role, Markeda will provide coordination support to the McLaren Center for Research Innovation (MCRI) and Research Integrity (RI) departments. Her responsibilities will include coordination of the daily activities associated with the research protocols and all facets of protocol management including regulatory compliance. In addition, Markeda will support research informatics and coordinate non-oncology research IT projects across the system.


Tamara Leo

The division of Clinical Excellence would like to welcome **Tamara Leo** to the position of Corporate Administrative Assistant.

Tamara received a Bachelor of Science degree from Walsh College and brings to the team over eight years of administrative assistant experience.

Tamara will be providing support to Vice President, Chandan Gupte, and Director of Corporate Research Administration, Lana Gevorkyan and Corporate Quality Director, Danette Hayman.

Please join us in welcoming Tamara as our newest team member.

NEW IRB MEMBERS


Kristine Hetzel

We would like to welcome **Kristine Hetzel** as a new member of the MHC IRB. Kristine is the Corporate Manager for McLaren University and joined the McLaren IRB effective February 1, 2018. Kristine is a registered nurse who obtained her Masters of Science in Nursing at Chamberlain College of Nursing in Illinois. Welcome Kristine!

WELCOME JULIE EARBY


Julie Earby

We would like to welcome **Julie Earby** as a new member of the MHC IRB. Julie is an Inpatient Pharmacist at McLaren Port Huron and joined the McLaren IRB effective May 1, 2018. Julie obtained her Doctor of Pharmacy from Ferris State University. Welcome Julie!

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