About the Research Publication Series:

The Medical College of Wisconsin is a major national research center and the second-largest research institution in Wisconsin. Basic science, clinical, and translational researchers thrive in the unique setting of an academic medical center. The innovative work of our scientists leads to groundbreaking discovery that impacts healthcare and saves lives. The Research Publication Series is a sampling of recent publications by faculty, staff, and student investigators.

MCW Collaborative Highlights, indicated with the puzzle piece icon, call out articles that are produced by multidisciplinary teams. These articles represent collaborative efforts between researchers from different departments, centers, divisions, or fields of study.

Publication Stats: July 2019

<table>
<thead>
<tr>
<th>Publication Type</th>
<th>June Total</th>
<th>Publications in Top Quartile Journals</th>
</tr>
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<tbody>
<tr>
<td>Articles</td>
<td>102</td>
<td>77 out of 128 (60.2%)</td>
</tr>
<tr>
<td>Editorial Material</td>
<td>13</td>
<td></td>
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<tr>
<td>Reviews</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
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Publications Fiscal Year to Date: 1,645

Publication stats are pulled by the MCW Libraries for the previous month using the Science Citation Index and Social Sciences Citation Index. For inclusion, one or more authors must be institutionally affiliated with MCW. Letters and abstracts are excluded from the data. The MCW Fiscal Year runs from July 1 – June 30.
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July 2019

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“Disseminated Blastomycosis in a Teenager Presenting with Pleural Effusion and Splenomegaly”

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“Efficacy of Salvage Chemotherapy in Diffuse Large B Cell Lymphoma with Primary Treatment Failure According to Putative Cell of Origin”

NEW FEATURE: MCW Interdisciplinary Collaborative Research Network

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Cover Image from “Synchronous Pancreatic Tumors in a Patient with History of Wilms Tumor: A Case of Pancreatic Adenocarcinoma and Lipid-Rich Neuroendocrine Tumor Diagnosed by Cytopathology”
I am an Assistant Professor within the Center for AIDS Intervention Research and Department of Psychiatry and Behavioral Medicine at MCW. I received my MPH and PhD degrees from the Zilber School of Public Health at the University of Wisconsin-Milwaukee and completed a postdoc in biostatistics and behavioral science at Hunter College of the City University of New York. My research focuses on prevention of HIV and other sexually transmitted infections (STIs) using behavioral, biomedical, and technology-based platforms to reduce HIV/STI disparities. I am particularly interested in research related to HIV pre-exposure prophylaxis, HIV self-testing, patient-delivered partner STI therapy, mHealth strategies for HIV prevention, and understanding the intersection of drug use and HIV transmission risk.

“Decisional Balance and Contemplation Ladder to Support Interventions for HIV Pre-Exposure Prophylaxis Uptake and Persistence”


Pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV. We aimed to develop and validate tools to support PrEP uptake interventions and document disparities in PrEP use among our nationwide sample of gay and bisexual men (GBM). The PrEP decisional balance and PrEP contemplation ladder were reliable and valid measures, providing brief assessment tools useful for interventions. Compared to White GBM, Black GBM had higher agreement in the health benefits of PrEP, but this did not translate to a higher position on the PrEP cascade and contemplation ladder closer to uptake. GBM with less than $50K/year annual income were lower on the PrEP cascade and contemplation ladder, highlighting the influence of structural barriers to PrEP uptake and continued engagement in daily dosing and quarterly HIV/STI testing required with PrEP.

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Table 1. PrEP decisional balance construct scores by race/ethnicity among gay and bisexual men objectively identified as candidates for PrEP (n = 545)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Health Benefits (range: 0-4; α = .91)</th>
<th>Social Benefits (range: 0-4; α = .72)</th>
<th>Health Consequences (range: 0-4; α = .82)</th>
<th>Social Consequences (range: 0-4; α = .86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2.56 (0.99)***</td>
<td>1.44 (1.17)</td>
<td>2.28 (1.11)</td>
<td>0.78 (1.11)</td>
</tr>
<tr>
<td>Latino</td>
<td>2.45 (1.00)†</td>
<td>1.39 (0.98)</td>
<td>2.46 (1.06)†</td>
<td>0.88 (1.06)†</td>
</tr>
<tr>
<td>White</td>
<td>2.14 (0.98)†</td>
<td>1.33 (0.98)</td>
<td>2.08 (1.05)†</td>
<td>0.71 (0.92)†</td>
</tr>
<tr>
<td>Other/Multiracial</td>
<td>2.38 (1.02)†</td>
<td>1.68 (1.13)</td>
<td>2.55 (1.06)†</td>
<td>0.84 (0.93)†</td>
</tr>
</tbody>
</table>

Notes: * p < 0.05; ** p < 0.01; *** p < 0.001; † superscripts denote posthoc comparison tests using Scheffe multiple comparisons adjustment. For health benefits, Black and Latino are not significantly (α = 0.05) different from each other, but Black and Latino are significantly different than White individually, and Other/Multiracial are not significantly different than any other category.
As a public health researcher, I aim to understand and reduce the racial disparities in HIV experienced by young Black, gay, bisexual, and other men who have sex with men. My research examines how multiple intersecting stigmas, including racism and homonegativity, influence HIV risk and prevention. Additionally, I use community-based participatory research approaches to understand other health disparities affecting marginalized populations. I have a particular interest in research with individuals who are unstably housed or homeless, marginalized adolescents and young adults, and the LGBTQ populations.

“Multiple Marginality and the Variation in Delinquency and Substance use Among Adolescent Gang Members”


This study examined family, school, and neighborhood factors that contribute to or protect against delinquency and substance use among African American and Latino adolescent gang members in Milwaukee (n=449). Our results demonstrated the protective effects of several family-level factors; increased family communication, monitoring, and parental investment were associated with lower levels of substance use and delinquency among current gang members. The school environment was also protective; adolescents who felt safe at school and had greater school involvement had lower levels of delinquency. Finally, several neighborhood factors were associated with increased delinquency including greater neighborhood disorder and greater police contact.

Table 3. Multivariate Associations between Risk and Protective Factors and Criminal Involvement, Delinquency, Drug Distribution, Substance Use, and Sexual Violence Perpetration for Adolescent Gang Members (N = 449)

<table>
<thead>
<tr>
<th>COVARIATES</th>
<th>HED (days) IRR (SE)</th>
<th>Marijuana (days) IRR (SE)</th>
<th>Any hard drugs IRR (SE)</th>
<th>Arrest IRR (SE)</th>
<th>Delinquency IRR (SE)</th>
<th>Drug distribution IRR (SE)</th>
<th>Sexual violence IRR (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.09 (0.19)</td>
<td>1.23 (0.15)*</td>
<td>1.87 (0.46)**</td>
<td>1.22 (0.12)*</td>
<td>0.91 (0.07)</td>
<td>1.09 (0.10)</td>
<td>0.32 (0.15)**</td>
</tr>
<tr>
<td>Age</td>
<td>1.23 (0.09)**</td>
<td>1.05 (0.05)</td>
<td>1.12 (0.09)</td>
<td>1.11 (0.04)**</td>
<td>0.97 (0.03)</td>
<td>1.01 (0.03)</td>
<td>1.42 (0.24)**</td>
</tr>
<tr>
<td>Race (ref: Black)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>1.38 (0.25)*</td>
<td>1.07 (0.15)</td>
<td>1.12 (0.31)</td>
<td>0.88 (0.10)</td>
<td>0.88 (0.08)</td>
<td>1.18 (0.13)</td>
<td>1.01 (0.65)</td>
</tr>
<tr>
<td>Other race</td>
<td>0.59 (0.16)*</td>
<td>1.19 (0.21)</td>
<td>1.27 (0.46)</td>
<td>1.02 (0.12)</td>
<td>1.01 (0.10)</td>
<td>0.84 (0.11)</td>
<td>0.79 (0.50)</td>
</tr>
<tr>
<td>Financial stress</td>
<td>0.98 (0.06)</td>
<td>1.03 (0.05)</td>
<td>1.18 (0.10)*</td>
<td>1.00 (0.03)</td>
<td>0.95 (0.02)*</td>
<td>1.01 (0.04)</td>
<td>0.83 (0.14)</td>
</tr>
<tr>
<td>Years in gang</td>
<td>1.02 (0.03)</td>
<td>1.02 (0.01)</td>
<td>1.06 (0.04)*</td>
<td>1.01 (0.01)</td>
<td>1.00 (0.01)</td>
<td>1.01 (0.01)</td>
<td>1.00 (0.05)*</td>
</tr>
<tr>
<td>FAMILY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lives with parent/guardian</td>
<td>1.00 (0.18)</td>
<td>0.89 (0.11)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Family communication</td>
<td>0.87 (0.05)*</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Family monitoring</td>
<td>1.01 (0.06)</td>
<td>0.91 (0.04)*</td>
<td>--</td>
<td>--</td>
<td>1.00 (0.03)</td>
<td>0.94 (0.03)*</td>
<td>--</td>
</tr>
<tr>
<td>Parental investment</td>
<td>0.93 (0.07)</td>
<td>1.14 (0.06)**</td>
<td>--</td>
<td>--</td>
<td>0.94 (0.03)*</td>
<td>--</td>
<td>0.86 (0.16)</td>
</tr>
<tr>
<td>Parent/guardian drug use</td>
<td>1.34 (0.27)</td>
<td>0.98 (0.16)</td>
<td>2.79 (0.95)**</td>
<td>1.02 (0.12)</td>
<td>1.02 (0.09)</td>
<td>1.31 (0.14)**</td>
<td>2.29 (1.40)</td>
</tr>
<tr>
<td>Parent allows adolescent sub. use</td>
<td>1.31 (0.27)</td>
<td>1.48 (0.23)*</td>
<td>1.36 (0.42)</td>
<td>1.13 (0.13)</td>
<td>1.19 (0.10)*</td>
<td>1.28 (0.13)*</td>
<td>4.12 (1.15)</td>
</tr>
<tr>
<td>Family gang involvement</td>
<td>1.01 (0.05)</td>
<td>1.02 (0.03)</td>
<td>1.05 (0.06)</td>
<td>1.04 (0.03)*</td>
<td>1.00 (0.02)</td>
<td>0.95 (0.10)</td>
<td>--</td>
</tr>
<tr>
<td>Parent/guardian incarceration</td>
<td>1.07 (0.20)</td>
<td>1.17 (0.14)</td>
<td>1.61 (0.44)*</td>
<td>1.12 (0.13)</td>
<td>1.07 (0.08)</td>
<td>1.01 (0.11)</td>
<td>3.26 (1.77)*</td>
</tr>
<tr>
<td>SCHOOL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled in school</td>
<td>1.04 (0.23)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Feels safe at school</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.80 (0.06)**</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>School involvement</td>
<td>0.80 (0.10)*</td>
<td>0.96 (0.10)</td>
<td>--</td>
<td>--</td>
<td>0.85 (0.05)**</td>
<td>0.93 (0.07)</td>
<td>--</td>
</tr>
<tr>
<td>NEIGHBORHOOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collective monitoring</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Police interactions</td>
<td>1.34 (0.09)**</td>
<td>1.13 (0.06)*</td>
<td>1.43 (0.14)**</td>
<td>1.36 (0.06)**</td>
<td>1.25 (0.04)**</td>
<td>1.19 (0.05)**</td>
<td>--</td>
</tr>
<tr>
<td>Neighborhood disorder</td>
<td>1.00 (0.14)</td>
<td>1.26 (0.13)*</td>
<td>1.26 (0.26)</td>
<td>--</td>
<td>--</td>
<td>1.29 (0.05)**</td>
<td>--</td>
</tr>
<tr>
<td>R²</td>
<td>--</td>
<td>--</td>
<td>0.32**</td>
<td>--</td>
<td>--</td>
<td>0.44**</td>
<td>--</td>
</tr>
</tbody>
</table>

*** p < .001  ** p < .01  * p < .05  .p < .10

Incident rate ratios (IRR, from multivariate Poisson and negative binomial regressions) or odds ratios (ORs, from multivariate logistic regressions) are reported along with standard errors (SEs).

Analyses were performed on 100 multiply imputed datasets and account for clustering by referral. R² values are not available for Poisson and negative binomial regressions. Sub. use = alcohol/drug use; HED = heavy episodic drinking.
I joined the Division of Biostatistics at MCW in 2017. My research expertise is statistical data analysis using different types of omics data, including single nucleotide polymorphism (SNP), copy number variation (CNV), DNA methylation, gene expression, proteomics (peptide), and metabolomics. I am particularly interested in developing statistical methodologies/tools in the fields of statistical genetics, bioinformatics, power and sample size calculation, integrative/meta-analysis and supervised/unsupervised machine learning problems. My major collaborators include the Departments of Pediatrics and Biomedical Engineering.

“RNASeqDesign: A Framework for Ribonucleic Acid Sequencing Genomewide Power Calculation and Study Design Issues”

Next generation sequencing (NGS) technology has emerged as a powerful tool in characterizing genomic profiles. Among many NGS applications, RNA sequencing (RNA-Seq) has gradually become a standard tool for global transcriptomic monitoring. Although the cost of NGS experiments has dropped constantly, the high sequencing cost and bioinformatic complexity are still obstacles for many biomedical projects. In addition to sample size, sequencing depth also directly relates to the experimental cost. Consequently, given total budget and pre-specified unit experimental cost, the study design issue in RNA-Seq is conceptually a more complex multi-dimensional constrained optimization problem rather than one-dimensional sample size calculation in traditional hypothesis setting. In this paper, we propose a statistical framework, namely “RNASeqDesign”, to utilize pilot data for power calculation and study design of RNA-Seq experiments.
Colleen Trevino, NP, PhD
Assistant Professor
Nurse Practitioner
Department of Surgery
Division of Trauma and Acute Care Surgery
Medical College of Wisconsin

I have been a nurse practitioner with the Division of Trauma and Acute Care Surgery for 17 years. In my clinical practice, I primarily manage Trauma and Acute Care Surgery patients through the continuum of admission to follow up and recovery. My research interests coincide with our division’s surgical specialties of Trauma Surgery and Emergency General Surgery. I have been investigating predictors, biomarkers, and biopsychosocial model development in the transition of acute to chronic pain in trauma patients. My Acute Care Surgery focus has been to investigate diagnosis and management of small bowel obstruction, antibiotic use in complicated appendicitis, fast-track discharge for acute appendicitis and laparoscopic cholecystectomy, and enteric fistula management.


Our institution developed and implemented an adhesive SBO protocol using evidence-based guidelines. A prospective cohort of SBO patients after implementation of the SBO protocol was compared to a historical cohort of SBO patients prior to the protocol. Patients without a history of abdominal surgery were excluded. Univariate analyses performed demonstrated a statistically significant decrease in both LOS by 1.35 days and in the proportion of patients receiving surgery (37% vs 25%). There was a decrease in time to surgery, rate of SBR, and rate of complications, yet there was an increase in rate of readmission, although these findings were not statistically significant. Utilizing an evidence-based SBO protocol leads to shorter LOS and may result in fewer operations for adhesive SBO patients.
“Two Weeks of Ischemic Conditioning Improves Walking Speed and Reduces Neuromuscular Fatigability in Chronic Stroke Survivors”


Motor recovery in stroke survivors generally plateaus six months post-stroke, and exercise training and treadmill training in the chronic stroke period (>6 months post-stroke) generally results in only modest improvements in walking speed. This pilot study was the first to demonstrate that ischemic conditioning both improves self-selected walking speed and reduces paretic muscle fatigue in stroke survivors. Further, the improvement in walking speed we observed exceeded what is considered a minimal clinically important difference (>0.10 m/s) for stroke survivors. Ischemic conditioning has been shown to be safe in numerous patient populations, can be accomplished at home or at the bedside in only 45 min, and requires no specialized training. Future larger studies are warranted to determine the efficacy of ischemic conditioning as a neurorehabilitation therapy or therapy adjunct post-stroke.

Changes in self-selected walking speed, as assessed by the 10-m walk test, in chronic stroke survivors after 2 weeks of either ischemic conditioning (IC) or IC Sham training on the paretic leg. In the IC-training group, self-selected walking speed increased from 0.86±0.21 to 1.04±0.22 m/s, whereas no change was observed in the IC Sham group (0.92±0.47 m/s pre-IC Sham vs. 0.96±0.46 m/s post-IC Sham). Data are shown as means ± SD. NS, not significant. *P < 0.05 pre-IC vs. post-IC.

Changes in isometric knee extensor muscle fatigability, as assessed the time study participants could sustain an isometric contraction equal to 30% of their maximum voluntary contraction, in chronic stroke survivors after 2 weeks of either ischemic conditioning (IC) or IC Sham training on the paretic leg. Time to muscle fatigue increased from 278±163 to 496±313 s in the IC group (P < 0.05), whereas no change was observed in the IC Sham group (397±202 s pre-IC Sham vs. 355±195 s post-IC Sham; P = 0.46). Data are shown as means ± SD. NS, not significant. *P < 0.05 pre-IC vs. post-IC.
Blastomycosis is caused by a fungus endemic to states and providences bordering the Lawrence Rivers and the Great Lakes. This case report pertains to healthy 16-year-old patient. He presented with a chief complaint of flank pain, emesis, and cough. He was found to have a left thigh abscess, left pleural effusion, and bony lesions in the lumbar spine and ribs. Infectious studies lead to a diagnosis of disseminated blastomycosis, and he was successfully treated with amphotericin B and transitioned to itraconazole. Given the non-specific nature of this condition, a high level of suspicion is required for diagnosis.

“Yap Is Required for Scar Formation but not Myocyte Proliferation during Heart Regeneration in Zebrafish”


Our group identified an unexpected role for Hippo-Yap signaling in extracellular matrix production and scar remodeling/resolution during zebrafish cardiac regeneration. We found compared to wildtype, yap mutant zebrafish displayed striking irregularities in extracellular matrix deposition and scar formation and increased immune cell infiltration in response to cardiac cryoinjury. These finding were further supported by siRNA mediated knockdown of Yap and subsequent RNA sequencing analysis in primary rat neonatal cardiac fibroblasts or cardiomyocytes. Yap knockdown in primary fibroblasts, but not cardiomyocytes, resulted in significant suppression of genes known to promote myofibroblast activation/matrix production while monocyte chemotaxis genes were significantly upregulated. Collectively our findings, suggest that Hippo-Yap signaling may function in multiple cell types to coordinate the processes underlying scar formation during cardiac regeneration. By understanding the cell specific role of Hippo-Yap, we hope to tailor therapeutic strategies for heart repair in humans.
Pancreatic β-cells Detoxify H2O2 through the Peroxiredoxin/thioredoxin Antioxidant System


Pancreatic beta-cells, which secrete insulin in response to a rise in blood glucose levels, become dysfunctional during the development of diabetes mellitus, contributing to hyperglycemia. This beta-cell failure is thought to be partially driven by oxidative stress, or damage caused by accumulation of reactive oxygen species, such as hydrogen peroxide. However, in this study, we demonstrate that beta-cells possess a robust antioxidant system, which requires thioredoxin reductase, and that protects them from DNA damage, depletion of intracellular energy stores, and death caused by continuous delivery of hydrogen peroxide. Our results challenge the widely-held view that beta-cells are particularly vulnerable to oxidative stress.

Synchronous Pancreatic Tumors in a Patient with History of Wilms Tumor: A Case of Pancreatic Adenocarcinoma and Lipid-Rich Neuroendocrine Tumor Diagnosed by Cytopathology


Although there is a higher incidence of secondary malignant neoplasms in patients with history of Wilms tumor (WT), pancreatic tumors are very infrequent in this population. We report the first case of synchronous pancreatic tumors in a patient with history of WT. Two separated pancreatic lesions were identified by abdominal CT scan. Fine-needle aspiration was performed. A pancreatic adenocarcinoma was diagnosed in the head of pancreas. The pancreatic body lesion was found to be a neuroendocrine tumor, which had characteristic vacuolated lipid-rich cytoplasm. Further molecular testing was done on both tumors, but no common cancer-associated mutation was found.
This work critically reviewed the diagnostic entity known as chronic traumatic encephalopathy (CTE) in comparison to other well-established neurodegenerative entities in five pertinent areas: 1) historical perspective, 2) guideline formation, 3) clinical diagnostic criteria, 4) pathological diagnostic criteria, and 5) validation studies of diagnostic criteria. Comparisons indicated that CTE is a disease in the earliest stages of formation and has yet to undergo rigorous development and refinement similar to other neurodegenerative diseases. Means to revise the current pathological diagnostic criterion and formulate antemortem clinical diagnostic criteria for CTE that would be consistent with the development of other well-established neurodegenerative diagnoses are discussed. Advancement in these areas will improve our understanding of long-term outcomes associated with repetitive head impacts/mild traumatic brain injury.

In this study we compared the outcomes of PTF DLBCL patients relative to two different platinum-based first salvage chemotherapy regimens. We further evaluated the outcomes of patients in different treatment groups based on the putative COO. In this high-risk population of PTF DLBCL we did not find any significant advantage of commonly used platinum-based combination chemotherapy regimens, including within GCB DLBCL cohort as reported in previous study. Continuing to identifying distinctive genetic alterations, dysregulated signaling pathways, or surface proteins that can be targeted with novel therapies will be critical to improve the outcome of these high-risk patients.
MCW Interdisciplinary Collaborative Research Network

The ICRN project was initiated by a 2017-2018 MCW Leadership Academy team to enhance visibility of MCW investigators and promote interdisciplinary collaboration to increase funding success. The Office of Research is pleased to support this interactive, promotional opportunity for MCW investigators and centers to find collaborators on campus. The profiles linked below have been voluntarily submitted by individuals and programs seeking collaborators.

Interdisciplinary Collaborative
MCW Research Network

Stephanie Olivier-Van Stichelen, PhD
 SEEKING
 • Human nutrition in pregnancy, lactation, & early development
 • Human microbiome

OFFERING
 • Mouse models of early developmental defect
 • Artificial sweeteners
 • Glucose dependent signaling (O-GlcNAcylation)

Recently published “Maternal exposure to non-nutritive sweeteners impacts progeny’s metabolism and microbiome”
CONTACT: solvier@mcw.edu

Interdisciplinary Collaborative
MCW Research Network

Svetlana Zharrova, FNP, PhD
 SEEKING
 • Clinical expertise in cardio-oncology & hypertension
 • Heart failure with preserved EF

Currently submitting “Heart Failure Self-Management testing the Individual and Family Self-Management Theory”
CONTACT: szharov@mcw.edu

Interdisciplinary Collaborative
MCW Research Network

QHS Data Coordinating Center

Pepsi Simpson, PhD
Professor and Director,
Quantitative Health Sciences

SEEKING
 • Multi-center Studies
 • Clinical Trials
 • Complex Trials

OFFERING
 • Data Management
 • Monitoring Study Design
 • Study Analysis


CONTACT: psimpson@mcw.edu

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