Methodist Research Institute

Research Day 2014

Poster Abstracts
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Real World Experience with Metric #37: Retrospective Analysis of Post PCI Bleeding Rates in a Statewide Healthcare System

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Metric #37, Risk Adjusted Bleeding, defines bleeding as: Any of the following occurring within 72 h after PCI or before hospital discharge (whichever occurs first): site-reported arterial access site bleeding, which may be either external or a hematoma >10 cm for femoral access, >5 cm for brachial access, or >2 cm for radial access; retroperitoneal, gastrointestinal, or genitourinary bleeding; intracranial hemorrhage; cardiac tamponade; post-procedure hemoglobin decrease of 3 g/dl in patients with a pre-procedure hemoglobin level <=16 g/dl; or post-procedure nonbypass surgery-related blood transfusion for patients with a pre-procedure hemoglobin level >=8 g/dl.

Summary Statement
Initial observed performance outcomes at IU Health’s largest institution, Methodist Hospital, were greater than desired for our post PCI risk adjusted bleeding events. As our quality improvement team began to look at our individual patients that were classified as a bleeding event in Metric #37, we found unexpected local trends in our 2011 data. Frail elderly women were not the majority of our observed post PCI bleeding events; this population accounted for approximately 12% of our post PCI bleeding event. Males under the age of 70 were over 50% of our post PCI bleeding events. We also observed that over 22% of our postprocedural bleeding events reported radial/ulnar access sites; this was also an unexpected observation. Our greatest opportunities for improvement were with blood transfusions and hemoglobin decreases greater than 3 gm. This discovery was unexpected and didn’t align with published research / national trends. In an effort to improve safety we undertook a retrospective review to understand why our bleeding rates were higher than expected.

ABSTRACT

Indiana University Health is a 17 facility system in which 9 sites report CathPCI Registry® procedures to the National Cardiovascular Data Registry (NCDR®). When reviewing the system results for Metric 37, our institutional bleeding rates exceeded the CathPCI Registry 90th Percentile of 1.61% at all 9 sites and the CathPCI Registry 50th Percentile of 3.67% at 7 of the 9 locations. Radial and femoral procedural access sites had comparable observed bleeding rates with the expanded lens of post PCI Bleeding for Metric #37.

The team analyzed 3,701 patients within our health system who had PCI procedures in 2012. Variables were analyzed to best replicate those in the NCDR CathPCI registry, Metric 37. Among the multiple variables analyzed, major surgery during the same episode of care as the PCI (t(78) = 3.73, p=0.000) was statistically significant. Of the bleeding, 53% occurred in males. Four anticoagulation therapies were independently analyzed and only two were found to be statistically significant – Bivalirudin and IIbIIIa.

Approximately one half of the bleeding events by definition were attributed to patients who received RBC transfusion. Of that subset, 58.7% (37/63) were anemic.
at the time of transfusion without evidence of any overt bleeding. In the statewide analysis, 67% (63/94) of the RBC transfusions were not associated with a hemoglobin drop or other defined bleeding event. Of those 63 patients, 28 patients or 44% of the patients were reported as having a ‘major surgery’ during the same episode of care as the PCI.

Further analysis revealed that 86.6% of the observed bleeding events were attributed to transfusion and/or an observed hemoglobin decrease of > 3 gm, not attributed to a specific anatomic location according to the patient’s record. Our institutional guidelines recommend a hemoglobin trigger of an Hgb < 8 g/l for RBC transfusion. The statewide data analysis showed that 44% of the RBC transfusions were completed with the pre-transfusion greater than 8 gm.

Conclusions
Our quality improvement team found physician and leadership education was the best approach to change our post PCI bleeding rates. Historically, vascular injury was how most physicians and clinicians classified post PCI bleeding. The total observed bleeding events, as defined by Metric #37, was an educational opportunity that had to occur before performance could be improved.

Prior to our project, it was thought that transitioning access site utilization to radial would decrease the post PCI bleeding rates. Our Lean Six Sigma project revealed that approximately 10% of the bleeding rates were access site related. Our greatest areas to improve were in the areas of RBC transfusions and hemoglobin decreases. Combined these areas accounted for 86% of the observed bleeding events. We developed physician specific slides to demonstrate the difference between PCI vascular injuries and post PCI bleeding events. This visual demonstrated the difference of the PCI “cause and effect” vascular injury metric to the “observed events” for Metric #37.
The second area that we undertook to improve our post PCI bleeding rates was RBC transfusion. We compared our reported hemoglobin at transfusion to those our organizational RBC transfusion guidelines and found a large opportunity for improvement. 41/93 RBC transfusion post PCI occurred when reported hemoglobin values were above 8 grams. Our 2012 physician specific scorecards included individual performance for adherence to the RBC transfusion guidelines. After the distribution of the physician specific scorecards, we observed an overall decrease in RBC transfusion at Methodist. Our entire PCI population observed a 36% decrease in post PCI transfusion (2012=73, 2013= 47). There was a 75% decrease in patient transfused when their hemoglobin values were greater than 8 grams (2012=28, 2013=7).

The raw number of post PCI bleeding events continues to decrease at Methodist Hospital. Preliminary performance illustrates a 50% decrease in events from CY2012 compared to CY2013 (2012= 96, 2013= 48 prelim). In addition, we continue to observe improvement in our Risk Adjusted Bleeding performance: CY2011= 6.51%, CY 2012= 5.84%, Q3 2013= 3.37% (Q3 2013 performance includes metric adjudication).

Significant process improvements and transparencies have changed the way post PCI care is provided. Future opportunities to continue our performance improvement have been identified for Metric #37. Our quality improvement team is currently developing an anticoagulation algorithm and investigating causes for the unexplained hemoglobin decreases post PCI.
Temporal Occurrence and Recurrence Patterns of Hypoglycemia During Hospitalization

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ABSTRACT

Hyperglycemia with or without a history of diabetes is common in hospitalized patients and is associated with increased morbidity and mortality. The treatment of hyperglycemia with insulin or oral agents involves the risk of hypoglycemia, which may be associated with poor clinical outcomes, and efforts should be made to minimize the risk of hypoglycemia during hospitalization. Previous studies have suggested a temporal pattern to hypoglycemia, and we reviewed audit data of hypoglycemia (blood glucose (BG)<50 mg/dL) in adult patients at two academic health centers from July, 2012 to June, 2013 to study the temporal occurrence and recurrence of hypoglycemia during hospitalization.

During the audit period, 274 index hypoglycemic episodes were identified. The mean age of the patients was 53.8 years with roughly equal gender distribution (male 47%, female 53%). 46% of the index hypoglycemic events occurred in the intensive care unit (ICU) while the remainder occurred on the general medical/surgical floor or progressive care unit. A recurrence of hypoglycemia (repeat BG <50 mg/dL between 1 and 24 hours following the index hypoglycemic event) occurred in 47 cases, with 12 cases of 3 or greater distinct hypoglycemic episodes separated by at least 1 hour during the 24 hour period. No patients on intravenous (IV) insulin experienced a recurrence of hypoglycemia while 80% of the patients who experienced a recurrence of hypoglycemia on subcutaneous insulin received basal insulin (glargine, detemir, NPH, or continuous subcutaneous insulin infusion). 197 hypoglycemic events were associated with the use of insulin or oral hypoglycemia agents, while 77 hypoglycemic episodes were found in patients without documentation of insulin or oral agents. Among the patients who received anti-hyperglycemic therapy, 84% received subcutaneous insulin, 15% received IV insulin, and 0.5% were on an oral agent alone. Of the patients who received subcutaneous insulin, 72% received basal insulin within twenty-four hours of the index hypoglycemic episode. To determine the temporal distribution of hypoglycemia, we compared the frequency of events that occurred in 6-hour intervals. Among patients receiving insulin or oral agents, 92 episodes occurred between midnight (MN) and 6AM, 43 episodes between 6AM and noon, 27 episodes between noon and 6PM, and 35 episodes between 6PM and MN. To control for the frequency of glycemic testing, we divided the total number of hypoglycemic events by the total number of BG readings for that time period and determined that hypoglycemia occurred more frequently between MN and 6AM and less frequently between noon and 6PM (p < 0.05) among patients receiving subcutaneous insulin. There was, however, no discernable diurnal pattern among patient receiving IV insulin.

Hypoglycemia may occur more frequently overnight and nocturnal glycemic testing should be considered during hospitalization. Patients that received basal insulin were most likely to experience a recurrence of hypoglycemia.
Vascular Complications Following Percutaneous Nephrolithotomy: 10 Years Of Experience

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ABSTRACT

Introduction and Objectives
Bleeding after percutaneous nephrolithotomy (PNL) is a significant complication with potential for major morbidity. The reported incidence of bleeding requiring transfusion following PNL is reported to be 1-11%. Our aim is to provide a contemporary look at vascular complications following PNL with access performed solely by a urologist using fluoroscopic guidance.

Material and Methods
After IRB approval, a retrospective review of 2792 patients who had undergone 3338 PNL between 2003 and 2013 at Indiana University Health Methodist Hospital and Mayo Clinic Rochester was performed. Patients who experienced significant bleeding requiring diagnostic renal angiography (RA) and subsequent superselective embolization (SSE) were reviewed and compared to the overall database.

Results
There were 15 patients (16 renal units) requiring RA and SSE (0.48%), ten patients were males, five were females. Eight kidneys had pseudoaneurysm (PA), four had arteriovenous fistula (AVF) and four had both. Mean time from PNL to bleeding was 7 days (range 1-15 days) and to SSE was 9.6 days (range 2-18 days). Cystoscopic clot evacuation was required in 26.6%. Mean drop in hemoglobin was 5.3 g/dl (range 2-9 g/dl). Transfusion was needed in 9 patients (60%). There were no differences between the vascular complications group (VCG) and the uneventful PNL group in mean age, (55.06 v 52.2 years, p = 0.519), history of UTI (40% v 38%, p = 0.92), history of previous urological procedure on the same renal unit (53.3% v 52.3%, p = 0.94), mean operative time (125.8 v 102.47 min, p = 0.192), the need for multiple access (18.75% v 18%, p = 0.939), and the location of renal access (lower pole punctures [76.4% v 70.6%, p = 0.911]). Mean intraoperative blood loss was 158.6ml (range 50-500ml). Interestingly, the VCG had a lower stone burden than the uneventful PNL group (stones > 2cm, 43.7% v 74.03%, p = 0.014).

Conclusion
Vascular injury associated with PNL is a rare yet serious complication. The incidence of vascular complications in this contemporary series is one of the lowest reported to date. We found that when PNL is performed at high volume tertiary care centers using urologist gained fluoroscopic renal access, the occurrence of vascular bleeding complications appears to be a random and rare event, as we were unable to identify any specific risk factors. However, early SSE avoided the need for blood transfusion in nearly half the patients.
Small conductance calcium-activated potassium channels specifically co-localizes with sympathetic nerve fibers in the stellate ganglion

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ABSTRACT

Introduction
Activation of small conductance calcium activated K (SK) current causes afterhyperpolarization and reduces neuronal discharges. SK upregulation may explain the reduced stellate ganglion nerve activity in dogs with vagal nerve stimulation (VNS). Whether or not SK protein co-localizes with tyrosine hydroxylase (TH) in sympathetic nerves remains unclear.

Methods
We studied 11 dogs, including 6 with VNS and 5 normal controls. Serial cross sections of left stellate ganglion were stained with TH and subtype 2 of SK protein (SK2). Cross sections of nerve bundles were analyzed to determine the number of pixels occupied by the positively stained nerves.

Results
We found that SK2 co-localized with TH (+) nerves in the nerve bundles, and was mostly absent from TH (-) areas (Figure). In the control group, SK2 (+) nerve and TH (+) nerve occupied 22584 ± 17116 and 15572 ± 15559 pixels (p = 0.51), respectively, with r value of 0.89 (p < 0.05). They accounted for 41.5 ± 11% and 30.3 ± 12.1%, respectively, of the cross sectional area. In the VNS group, SK2 (+) nerve and TH (+) nerve occupied 7634 ± 7026 and 10249 ± 16287 pixels (p = 0.73), respectively, with r value of 0.93 (p < 0.05). They accounted for 29.0 ± 22% and 26.3 ± 19%, respectively, of the cross sectional area.

Conclusion
The SK2 specifically co-localizes with TH in nerve bundles, suggesting that SK2 channels may regulate sympathetic nerve activity in the stellate ganglion.

Author Disclosures: Dr. Chen’s laboratory received equipment donations from Medtronic, St Jude and Cyberonics, Inc.
Lipschutz Ulcers: Uncharacteristic Adolescent Vaginal Dermatoses

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ABSTRACT

Case report of an unusual vulvar lesion and acute onset of vaginal pain in the adolescent female.

A 12 yo premenarchal female presents to the ED with a 1-day history of vaginal pain and ulceration. History was significant for prior apthous oral lesions and hip pain. She denied no trauma, abuse or sexual activity. Laboratory results and workup was negative. Examination and history were consistent with Lipschutz ulcer.
Quality Improvement and the Postpartum Visit: Increasing Attendance at a County Hospital and its Outlying Clinics

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ABSTRACT

Postpartum follow-up is an important part of the care of obstetric patients but studies show that postpartum visit rates are especially low among certain population subgroups. In an attempt to improve postpartum visit attendance rates among patients at a county hospital in Indianapolis, we introduced three interventions to address common barriers to care. Patients who delivered at Wishard hospital within a 5 month period in 2012 were either provided a handout describing the utility of the postpartum visit, had a postpartum visit scheduled for them prior to discharge or both. Compared to a control group receiving no intervention, postpartum clinic attendance rates improved with intervention. However, there was no statistically significant difference in postpartum attendance between the different interventions. These results suggest that small efforts to improve postpartum visit attendance may have large effects and that by continuing to address these barriers to care, we can improve the care of our patients in the postpartum period.
Enhanced anticancer properties of lomustine in conjunction with docosahexaenoic acid in glioblastoma cell lines

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ABSTRACT

Object
Glioblastoma multiforme (GBM) is a rapidly infiltrating tumor that consistently rematerializes despite various forms of aggressive treatment. Brain tumors are commonly treated with alkylating drugs, such as lomustine, which are chemotherapeutic agents. Use of these drugs, however, is associated with serious side effects. To reduce the side effects, one approach is to combine lower doses of chemotherapeutic drugs with other nontoxic anticancer agents. In this study, using glioblastoma cell lines, the authors investigated the anticancer effects of lomustine, alone and in combination with docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid normally abundant in the brain and known for its anticancer potential.

Methods
Cells were cultured from 3 human-derived tumor cell lines: U87-MG, DB029, and MHBT161, and supplemented with either DHA or lomustine to determine the growth inhibitory potential using WST-1, a mitochondrial functional indicator. Human-derived cerebral cortex microvascular endothelial cells served as a normal phenotypic control. Cellular incorporation of DHA was analyzed by gas chromatography. Using flow cytometric analysis, the DHA and/or lomustine affect on induction of apoptosis and/or necrosis was quantified; subsequently, the DHA and lomustine affect on cell cycle progression was also assessed. Western blot analysis confirmed the role of downstream cellular targets.

Results
U87-MG growth was inhibited with the supplementation of either DHA (ED50 68.3 mM) or lomustine (ED50 68.1 mM); however, growth inhibition was enhanced when U87-MG cells were administered equimolar doses of each compound, resulting in nearly total growth inhibition at 50 mM. Gas chromatography analysis of the fatty acid profile in DHA-supplemented U87-MG cells resulted in a linear dose-dependent increase in DHA incorporation (< 60 mM). The combination of DHA and lomustine potently induced U87-MG apoptosis and necrosis as indicated by flow cytometric analysis. Activation of caspase-3 and PARP was evident in lomustine-treated U87-MG cells, although this activation did not appear to be dependent on
DHA supplementation. Additionally, lomustine-treated cells growth arrested in the G2/M cell cycle stage, regardless of the presence of DHA. Similar to the U87-MG observations, the combination of DHA and lomustine resulted in growth inhibition of 2 additional human-derived GBM cell lines, DB029 and MHBT161. Importantly, in primary human-derived cerebral cortex endothelial cells, this combination was only growth inhibitory (40.8%) at the highest dose screened (100 mM), which indicates a certain degree of selectivity toward glioblastoma.

**Conclusion**
Taken together, these data suggest a potential role for a combination therapy of lomustine and DHA for the treatment of GBMs.
Cardiac Arrest Survival with Good Neurologic Outcome: Comparison of Initial Rhythm and Event Site

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ABSTRACT

Introduction
Induced hypothermia (IH) to 32-34°C is a recommended component of post cardiac arrest care. The impact of IH on outcome is well documented with shockable ventricular rhythms (VT/VF), but less clear with pulseless electrical activity (PEA) or asystole (AS). IH has been implemented for all unresponsive post arrest patients, without regard to arrest location or rhythm, at our institution since 2008.

Methods
A retrospective review of all unresponsive post cardiac arrest patients treated with IH was done. We included all in-hospital arrests (IHCA) and out-of hospital arrests (OHCA) from 2009-2012. Per protocol post-arrest IH was initiated in the emergency department for OHCA and in the intensive care unit for IHCA. Withdrawal of support & disposition was left to the discretion of the admitting team. We analyzed patient demographics, peri-arrest and treatment variables, survival to discharge, and neurologic outcome data for all patients. Good neurologic outcome (GNO) was defined as a cerebral performance category of 1-2 assessed at discharge.

Results: 580 patients who underwent IH were included: 478 OHCA (82.4%), 102 IHCA. VT/VF was the initial rhythm for 194 patients and 386 had PEA/AS (66.6%). Mean ROSC to goal temp was 284.7 ± 4.04 minutes (min) and mean IH initiation to goal temp was 179.7 ± 12.4 min. Within group survival was 42.9% for OHCA and 45.1% for IHCA; 63.9% for VT/VF and 32.9% PEA/AS. Overall survival with GNO was 31.3% (32.6% OHCA, 25.5% IHCA). Survival with GNO for VT/VF was 54.6% (56% of OHCA, 38.8% of IHCA) and 19.7% for PEA/AS (18.9% of OHCA, 22.6% of IHCA). For survivors to discharge (N = 124 VT/VF, N = 127 PEA/AS), 85% of VT/VF and 59.8% of PEA/AS survivors had GNO. The odds ratio [OR] for GNO among VT/VF survivors was 3.95 (95% CI 2.14-7.29, p < 0.0001) compared with PEA/AS survivors and all survivors, OR 0.25 (0.14-0.47, p < 0.0001).

Conclusions
We conclude that PEA/AS is a more frequently encountered initial rhythm for both OHCA and IHCA and that survival with GNO is achievable. While survival with GNO is less with PEA/AS, the trend for improved GNO with IH appears to be better than reported in the historical literature (7-12% survival; 1.7-10% with GNO).
Endothelial adaptation to hypothermia requires transient activation of the PERK pathway

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ABSTRACT

Understanding how human cells adapt to mild hypothermia may help develop new procedures for organ preservation at 0°C and transplantation. Our previous studies using human coronary artery endothelial cells (HCAECs) demonstrated that changes in intracellular catalytic iron pools, glutathione and ferritin contribute to cellular adaptation to mild hypothermia at 25-32°C and protection from 0°C-injury. Furthermore, our proteomic studies revealed that changes in protein expression are involved in such adaptation. We therefore hypothesized that endoplasmic reticulum stress (ER stress) is involved in initiating the cold-adaptation. Our results indicated that ER stress sensors PKR-like ER kinase (PERK) and Inositol-requiring enzyme 1α (IRE1α) are activated during the early phase of cold adaptation as indicated by their dissociation from BiP (Immunoglobulin heavy chain binding protein also known as glucose regulated protein 78). PERK activation also inhibited protein synthesis through activation of eIF2α. The role of ER stress in cold-adaptation is further confirmed by our findings that low doses of dithiothreitol (DTT) or thapsigargin (Tg), which induces ER stress, also protect at 0°C for 24-72h as detected by measurements of LDH release. In addition, protection induced by cold-adaptation at 32°C is attenuated by specifically inhibiting PERK with GSK 2606414. Prolonging PERK-induced phosphorylation of eIF2α with salubrinal protects cells from damage at 0°C. Inhibiting PERK with GSK2606414 also attenuates cold-induced glutathione increase, which is regulated through the antioxidant response element (ARE). The antioxidant transcription factor Nrf2, which binds to ARE, is activated during cold adaptation. Together, our results demonstrate involvement of PERK in cold-induced adaptation of cultured HCAECs.
Research Area: Regulation of immune, Stem and Cancer Cells of the Brain

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SUMMARY

The brain is the central organ of the nervous system that controls all physical, mental and social actions. The delicate nature of the human brain makes it susceptible to damage and diseases. The study of the brain dates back to ancient times, but the scientific study of the nervous system underwent a significant explosion in the second half of the twentieth century. Many aspects of the brain’s functions are still poorly understood. Neuroscience is a fascinating area of research in the 21st century that will revolutionize our perspectives on brain function and approaches to treat brain diseases. The Neuroscience Research Laboratory at Methodist Research Institute, Indianapolis investigates mechanisms in the regulation of immune, stem and cancer cells of the brain relevant to multiple sclerosis, inflammation, cancer, stem cell biology and autoimmune diseases.

Targeting inflammation in multiple sclerosis and neurodegenerative diseases

The immune system has evolved to discriminate self from non-self, thereby protecting the host from infection and malignancy. Nevertheless, a breakdown in this immune-regulatory process often results in the pathogenesis of chronic infectious diseases, malignant tumors and organ-specific autoimmune diseases. Multiple sclerosis (MS) is a neurological disorder that affects young adults and women more frequently than men. The etiology of MS is not known, but it is generally viewed as a myelin antigen-specific T cell-mediated autoimmune disease of the central nervous system (CNS). We investigate the mechanisms in the regulation of immune and inflammatory responses of the brain in multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis. We study the role of JAK-Stat signaling pathways in Th1/Th17 cell differentiation and its regulation by nuclear receptors, nutraceuticals and other small molecule inhibitors in EAE/MS. We investigate the role of inflammasome signaling in
the pathogenesis of multiple sclerosis and traumatic brain injury and its significance to the treatment of neuroinflammatory diseases.

**Neural stem cells and CNS repair**

Multiple sclerosis (MS), spinal cord injury and stroke are diseases of the central nervous system (CNS) that pose major health problems. Despite recent medical advances, there is no cure for these CNS diseases. The spontaneous recovery of multiple sclerosis, spinal cord injury, stroke and trauma is hindered by the limited ability of vertebrate CNS to regenerate lost cells, replace damaged myelin and re-establish the functional neuronal connections. Stem cells with self-renewal and multi-lineage differentiation property have the potential to replace or repair damaged CNS. While embryonic stem cells have unlimited potential to self-renew and differentiate into any type of cells, adult neural stem cells can grow and differentiation into all types of brain cells. The stem cells have the potential to restore defective and damaged cells of the brain. We develop strategies to isolate neural stem cells and study their use in the treatment of MS and other neurodegenerative diseases. We investigate the mechanisms in the regulation of oligodendrocyte differentiation of neural stem cells in culture and in the brain.

**Targeting brain tumor stem cells**

Brain tumors are the most devastating cancers that present unique challenges to therapy and pose major health problems. Despite recent advances in surgery, radiation, chemotherapy and other molecular therapies, a cure for brain tumors remains elusive. The multi-drug resistance and fast recurrence are some of the challenges in combating brain tumors. Cancer stem cells (CSCs) are a small population of cells in cancer tissue that show asymmetric division, self-renewal and tumor initiation capabilities. Cancer stem cells have been identified in many tumors including acute myeloid leukemia, breast, prostate, liver, colon, pancreas, skin, and brain cancer. The failure to cure brain cancer has been attributed to the fact that typical therapies target rapidly proliferating tumor cells, which respond transiently, while sparing the tumor stem cells, which have high tumorigenic potential. Brain tumor stem cells (BTSCs) are resistant to standard therapies and are considered responsible for the recurrence of brain tumors after radiation and chemotherapy in patients. There is no treatment available that can successfully target BTSCs in patients. Thus, further investigations are needed to identify new therapeutic targets for brain tumor treatment. We develop strategies to isolate and expand brain tumor stem cells to discover molecular targets for drug screening and therapy. We investigate the mechanisms in the regulation of stemness, differentiation and survival/death of brain tumor stem cells in culture and in the brain.
Cost-benefit Analysis of Home Blood Pressure Monitoring in Hypertension Diagnosis and Treatment: An Insurer Perspective

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ABSTRACT

Background
One in three people has high blood pressure (BP), making it the most common diagnosis in adults with direct costs projected this year to top $82 billion ($153 billion if cardiovascular diseases attributable to hypertension are included in the estimate).1 Successful management of hypertension must start with an accurate diagnosis. However, when evaluated solely on the basis of intermittent blood-pressures taken during doctor visits, the diagnosis of hypertension is prone to bias due to the “white-coat” effect (the tendency of some individuals with normal blood pressure to exhibit falsely high readings in a doctor’s office)2, and to “masked” hypertension (the tendency to exhibit normal blood pressures in the doctor’s office but abnormal blood pressures at home, especially during nighttime hours).3 White-coat hypertension affects 12-30% of patients4-5 and results in patients being put on unnecessary lifelong medications. Masked hypertension occurs in 10-23% of patients3 and results in the failure to treat true hypertension, thereby increasing the risk of costly downstream adverse events and end-organ damage. There is now a growing recognition that definitive diagnosis depends on assessing out-of-clinic BP values.6 Self-measured blood pressures taken by the patient at home are inexpensive and easy to obtain, and have been shown to be diagnostically superior7 and prognostically more predictive8-10 than conventional office blood pressures. However, despite over two decades of research demonstrating its effectiveness8,9,11-17 home blood-pressure monitoring continues to be underutilized. In 2005 only 55% of hypertensive patients reported using HBPM to monitor their BP.18 A possible reason for this is that most insurance companies do not reimburse for home monitors under the belief that it is not cost-beneficial, and lack of reimbursement discourages utilization. A recent national survey revealed that only 1 in 3 primary care providers recommends home blood-pressure monitoring routinely for all their hypertensive patients, and of the two-thirds who do not, the top reason given (by 43%) was the belief that the patient could not afford a home monitor.18 The premise of our study is that insurers would be more likely to pay for home monitors if they had evidence that it would make economic sense for them to do so. And if patient costs were fully reimbursed, adoption and use of home monitoring would likely increase, diagnostic accuracy would improve, rates of hypertension-related morbidity and mortality would fall, and money would be saved.

Study Methods
In this cost-benefit study we developed a decision-analytic simulation model from the perspective of the insurer. Model inputs were derived from 2008-2011 insurance claims data, and from the CDC’s 2009-2010 National Health and the Nutrition Examination Survey (NHANES) data and published meta-analyses. Our model simulates transitions among various health states from initial physician visit, to hypertension diagnosis, to treatment, to hypertension-related cardiovascular diseases, and patient death.
or resignation from the insurance plan. Once established, the model was used to estimate net dollars saved (savings minus costs) and return on investment (net savings divided by costs) attributable to home blood-pressure monitoring compared to clinic blood-pressure monitoring. Depending on the specific insurance plans and age-groups considered, we estimated that net savings would range from $33 to $166 per insurance-plan member in the first year, and from $415 to $1,364 per member in the long-run (10-years). Return on investment ranged from $0.85 to $3.75 per dollar invested in the first year, and from $7.50 to $19.34 per dollar invested in the long-run.

Conclusions
These findings suggest that it would be cost-beneficial for insurer’s to reimburse patients for the cost of home blood-pressure monitors. This is the first study to show that home-monitoring has positive economic value from a private-market perspective. By highlighting the return on investment that could be realized by insurers, our study helps support a business case for the reimbursement of home blood-pressure monitoring. Further clinical trials are needed to validate these simulated findings prospectively.

References
Leveraging 30 Operating Rooms to Simultaneously Maximize Elective Volumes and Assure Timely Service for Urgent and Emergent Cases using Computer Simulation

Karim Boustany, PhD and Larry Stevens, MD

Indiana University School of Medicine & Indiana CTSI

ABSTRACT

Background
The reality of increasingly limited healthcare resources challenges hospitals and operating rooms to operate at maximal efficiency.

Challenge
There exist a relatively large number of possible strategies for leveraging 30 operating rooms in order to simultaneously maximize elective volumes and assure timely service for urgent and emergent cases.

Solution
Develop a computer simulator that allows Indiana University Health Methodist Hospital to generate and test a large number of complex strategies in silico and provide the level of analytical decision support that healthcare leaders need.

Advantage
Computer simulators offer the ability to quickly provide insights into operational, financial, and health outcomes by experimenting safely with case volumes, specialty proportions, resource allocations, staffing levels, and more.

Method
Using industrial engineering techniques, we are able to accurately model perioperative areas as complex adaptive systems, connecting organizational functions and layers with external factors and evidence-based standards of care.

Conclusion
This poster illustrates the value of computer simulation in the context of strategic and tactical planning of surgical facilities.
Center for Health Innovation and Implementation Science Increases Value to Patients, Clinicians and Health Systems

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ABSTRACT

The National Institutes of Health reports that adoption of new research into routine clinical practice takes on average 17 years for only 14% of original research, ultimately affecting merely 1% of the target patient population and costing $1 billion. The Center for Health Innovation and Implementation Science (CHIIS) establishes a platform for disseminating and implementing evidence-based research within health systems to increase the value delivered to patients at the clinic, unit, hospital, and system levels. CHIIS uses innovation and implementation science tools to establish data-driven delivery systems, infrastructures and processes that drives system transformation and supports survival in an era of declining reimbursement and demand for accountability.
Is Age a Risk Factor for ICU Delirium? A Prospective Cohort study

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The Indiana University Delirium Study Group

ABSTRACT

Background
Delirium in the intensive care unit (ICU) is prevalent and is associated with high morbidity and mortality. Whereas age is an established risk factor for delirium outside the ICU, its effect on ICU delirium is unclear.

Objective
The purpose of our study was to evaluate the association between age and incident delirium in the ICU.

Methods
We performed a prospective, observational cohort study in the Medical Intensive Care Unit (MICU), Surgical Intensive Care Unit (SICU), and (PICU) Progressive Intensive Care Unit of an urban, university-affiliated public hospital. 2557 consecutively admitted patients were screened for delirium using the Confusion Assessment Method-ICU (CAM-ICU) within 24 hours of their admission and twice daily thereafter between May 2009 and October 2012. Incident delirium was defined as the first positive CAM-ICU after the initial negative CAM-ICU result. Patients were stratified into three groups based on their age (18-49 years, 50-64 years, and ≥ 65 years). Baseline characteristics such as race, gender, mean Acute Physiology Score (APS), hospital location, depression, hypertension, smoking history, alcohol history, narcotic use, benzodiazepine use, anticholinergic use, mean Richmond Agitation Sedation Scale (RASS), time of CAM-ICU, and insurance status were compared among the three groups. Multivariate analysis was used to adjust for all the relevant variables in the final analysis.

Results
There were 576 patients in 18-49 age group; 989 in the 50-64 age group, and 992 in the ≥ 65 age group. The delirium incidence was 5.9% in the 18-49 group, 5.5% in the 50-64 group, and 7.4% in patients 65 and older (p < 0.001). Odds ratio for incident delirium for age 18-49 compared to 65 was + 0.21 (CI: 0.12, 0.37), whereas the odds ratio for incident delirium for age 50-64 compared to 65 + was 0.25 (CI: 0.15, 0.42).

Conclusion
ICU patients aged 65 and over were 4.8 times more likely to develop delirium when compared to patients aged 18 to 49; and 4 times more likely when compared to patients aged 50-64. This has important implications for clinical staff and hospital administrators to direct efforts toward reducing the burden of delirium in elderly.

Financial Support: The study was supported by two grants from the National Institute on Aging (R01AG034205 and K23-AG043476) awarded to Drs. Bosutani and Khan.
Delirium in the ICU
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Indiana University School of Medicine & Indiana CTSI

ABSTRACT

Background
Delirium is a state of confusion thought to be caused by neurotransmitter imbalance in the brain (Ely & Girard, 2013). Studies have shown that the neurotransmitter imbalance could be caused by an excess of dopamine, an acetylcholine deficiency, and possible adverse reaction between dopamine and serotonin. Studies have found that between 50% and 80% of patients admitted to the ICU are found to have this condition. Delirium episodes in the ICU have been linked to additional problems such as longer hospital stays, higher risk of developing comorbidities and/or long-term neuropsychological deficits, and even a higher risk of death within the one year after their ICU stay.

Objective
Our answer to treating delirium has developed into three studies we (along with our partners) currently run in the ICU. These studies include Pharmacological Management of Delirium (PMD), Preventing Post-Operative Delirium in Esophagectomy and Pneumonectomy Patients (PE-POD), and Modifying the Impact of ICU-Associated Neurological Dysfunction (MIND-USA). We have also discovered through research that certain medications can increase the risk and severity of delirium by their anticholinergic effects. This information helped develop the Anticholinergic Cognitive Burden scale to help determine total effects on cognition (Boustani et al., 2012).

Design
All three studies are double-blinded randomized-controlled studies. The patients are identified in different ways: PMD are patients found to be delirious on RASS and CAM-ICU screening, PE-POD patients are enrolled before surgery in an attempt to prevent delirium from taking place, and MIND-USA patients are enrolled if they are on the ventilator and/or vasopressors and screened for delirium.

Setting
The setting for our three delirium trials are conducted in different places. PMD is research conducted in Eskenazi Hospital and University Hospital. It will soon be carried out in Methodist Hospital as well. PE-POD research is conducted only in University Hospital. MIND-USA research is conducted in University Hospital and Methodist Hospital.

Patients
The participants will be patients who are critically ill in the ICU. PE-POD patients are identified as those who are preparing for surgical treatment and then will be admitted to the ICU following surgery.
**Intervention**

PMD has two major arms: usual care and intervention. Usual care is just analysis of how the patients are treated by their physicians without any intervention. Intervention consists of haloperidol at a low dose of either 1 mg or 0.5 mg (depending on age) every eight hours and reduction of medications that are known to have an anticholinergic effect. Patients are monitored twice a day with the RASS, CAM-ICU, and a variety of other tools to assess for cognition, physical status, and side effects. We are currently running this project in Eskenazi Hospital, University Hospital, and Methodist Hospital.

PE-POD is a study in which patients are enrolled prior to surgeries for a pneumonectomy, esophagectomy, or thoracotomy in hopes of preventing delirium from occurring after surgery and transfer to the IC. After surgery, the patients receive either placebo or haloperidol three times a day as well as avoiding the use of anticholinergic medications. MIND-USA is a satellite study based upon the Vanderbilt study MIND (Ely & Gerard, 2013). We are one of 12 total sites involved in this project. The objective is to minimize the incidence of delirium in patients who are on the ventilator and/or vasopressors by using either placebo, haloperidol (a typical antipsychotic), or ziprasidone (an atypical antipsychotic). Patients are enrolled while on the ventilator and/or vasopressors. They have five days to become delirious. If the patient becomes delirious, they are given the medication which is titrated up to the highest dose. The patient is then titrated down after four clinical assessments that are found to be negative for delirium. Patients are monitored closely to make sure they are not given any other antipsychotics. Patients are monitored twice daily for delirium.

**Measurements**

All patients are assessed for signs of delirium with the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) tools (Boustani et al., 2012). Other tools are used in conjunction with these to assess the patient as their care continues.

**Conclusions**

These interventions may prove that haloperidol and/or ziprasidone in low doses are effective treatments to utilize as either a prophylactic measure or to try to alleviate delirium once it is detected. ICU staff are also being educated on the RASS and CAM-ICU administration techniques so they may properly detect delirium and report it to the physician or follow a standardized delirium protocol. We may also find clues in their blood by looking at biomarkers to determine what makes patients susceptible to becoming delirious while in the ICU.

**References**


ABSTRACT

Background
Five million Americans are admitted to intensive care units (ICU) annually due to life-threatening illness. Around 70% of mechanically ventilated patients will experience delirium during their stay in the ICU. Delirium generates $4-16 billion annually in associated costs in the U.S. and can lead to increased ventilator days, longer length of stay, increased mortality rate, and increased long-term neuropsychological deficits. Advances in the management of critical illness have increased the survival rate, however, as many as 50% of ICU survivors are left with newly acquired cognitive, physical and psychological impairments that can have devastating long-term consequences for both patients and their caregivers. Implementation of the “ABCDE” bundle, which consists of awakening (A) and breathing trial (B), choice of sedatives and analgesics (C), daily delirium monitoring (D), and early mobility (E), showed that mechanically ventilated patients were 3 times more likely to return to independent functioning at hospital discharge, and had shorter duration of delirium.

Objective:
The ABCDE Bundle consists of 5 interdependent components that help to address poor outcomes associated with: prolonged ventilator use, over sedation, and unrecognized delirium in this vulnerable population of patients.

Design
This is a quality improvement implementation project at IUH

Setting
Methodist and University Hospital Intensive Care Units

Patients
All ICU patients can receive one or more components of the ABCDE Bundle

Intervention
The bundle will be piloted in CMCC at Methodist hospital. The Center for Health Innovation and Implementation Science will hold an innovation forum with Methodist, University and Eskenazi to develop a streamlined way to deliver the ABCDE Bundle to all eligible ICU patients as standard of care.

Measurements
Ventilator days and incidences of Ventilator Acquired Pneumonia (VAP), hospital and ICU length of stay, costs associated with ventilator days, sedative use, delirium occurrences, morbidity, mortality, and patient and family satisfaction
SymTrak

Patrick Monahan, PhD • Amanda Harrawood, BS • Malaz Boustani, MD, MPH

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Indiana University School of Medicine & Indiana CTSI

ABSTRACT

Background
Currently no clinically practical (brief, publically available, easily scored,) multi-domain instruments exist that capture the ‘voice’ of both the informal caregiver and the patient when assessing symptoms of elderly patients who attend primary care with multiple chronic conditions. The new SymTrak (Symptom Tracker) will assess several domains of symptoms while being both research-valid and clinically practical.

Methods
This study is divided into three Phases. In the first phase, focus groups and cognitive interviewing were conducted with patient-caregiver dyads (n = 48) recruited from Eskenazi Health primary care, physicians (n = 14), and nurse practitioners (n = 12). In the second phase, Individual patients (n = 40) and patient-caregiver dyads (n = 40) are completing two versions of the current SymTrak in clinic to collect time-to-completion and preference data. In the third phase, individual patients (n = 200) and patient-caregiver dyads (n = 200) are being recruited to complete a battery of tests via phone interview (TICS, SymTrak, PHQ-8, GAD-7, PEG, Bakas Caregiving Outcomes Scale, Oberst Caregiver Burden Scale, HUI). For phase three, all participants will be assessed at baseline and 3-month follow-up; and a subset of 60 participants will be randomized for 24-hour retesting to assess test-retest reliability.

Preliminary Results:
The first phase has been completed and produced several themes resulting in substantial revision to the initial draft of the SymTrak tool developed by our expert panel. Physicians and nurses provided “big picture” feedback and suggestions for clinical practicality. Patients and caregivers provided many item-level useful suggestions that led to adding, dropping, or revising items.
P-38-Mapk Signaling and Intracellular Calcium Mobilization Converge into a Mitochondrial Pathway that Mediates Arachidonic Acid-Induced Human Brain Endothelial Cell Death

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ABSTRACT

Brain endothelial cells provide a dynamic interface between circulating blood and the brain parenchyma, and are essential for brain homeostasis. In addition to their participation in maintaining the integrity and function of the blood-brain barrier, brain endothelial cells play a critical role in supporting neuroaxonal growth and brain plasticity. Injuries to the brain endothelial cell lining, triggered by inflammation and other insults, can result in brain endothelial death, which contributes to the pathogenesis of diverse neurological disorders. Levels of arachidonic acid (AA), a bioactive fatty acid, dramatically increase during cerebral inflammation. However, its role in brain endothelial cell dysfunction remains elusive. The aim of this study was to characterize the mode of AA-induced brain endothelial cell injury and elucidate the underlying signaling pathways. Challenge of human brain endothelial cells with AA resulted in dose- and time-dependent cell detachment from the extracellular matrix followed by caspase-3 and caspase-7 activation. Activation of p38-mitogen activated protein kinase (MAPK) and subsequent phosphorylation of mitogen-activated protein kinase activated protein kinase 2 (MAPKAP-2) and heat shock protein-27 (Hsp-27) were also detected in response to AA. On the other hand, pharmacological inhibition of p38-MAPK prevented AA-induced cell detachment, and MAPKAP-2/Hsp-27 phosphorylation. RNA interference-mediated p38α or p38β suppression abrogated AA signaling to caspase-3 and Hsp-27, suggesting involvement of both p38 isoforms in AA-induced HBEC apoptosis. Hsp-27 silencing also blocked caspase-3 activation. AA increased intracellular calcium mobilization, which was attenuated by blockade of the inositol 1, 4, 5- trisphosphate receptor (IP3R). Similarly, AA-induced caspase-3 activation was abrogated by treatment with IP3R antagonists, while p38-MAPK activation was not affected. AA induced disruption of the mitochondrial transmembrane potential and release of cytochrome c, and these mitochondrial apoptotic signals were abrogated by inhibitors of both intracellular calcium mobilization and p38-MAPK activation. These findings are consistent with the involvement of p38-MAPK and IP3R-dependent calcium signaling in AA-induced brain endothelial cell detachment and apoptosis. While calcium did not mediate AA-induced p38-MAPK activation, both signals converged into a common mitochondrial death pathway. Taken together, these results highlight a previously unrecognized signaling cooperation mediating brain endothelial cell injury and death. Understanding the mechanisms controlling life and death of the cerebral endothelium may provide new therapeutic opportunities to achieve neuroprotection, enhance brain repair and decrease the burden associated with cerebrovascular disorders.
**Prostaglandin E2 Activates An Okadaic Acid-Sensitive Ser/Thr Phosphatase That Leads To Transient Inhibition Of The Erk 1/2 Pathway In Glioblastoma Multiforme**

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**ABSTRACT**

Glioblastoma multiforme (GBM) is among the most lethal of all human tumors. Despite aggressive therapy, the majority of patients die within 9-16 months from the initial diagnosis. There is, therefore, an urgent and unmet clinical need to develop novel therapeutic strategies to improve the treatment and prognosis of GBM patients. Prostaglandin E2, the most abundant prostaglandin produced by tumor cells and by the tumor microenvironment, plays a critical role in regulation of tumor cell functions by activating signaling pathways that ultimately lead to increased tumor growth, proliferation, invasion, and survival. We previously demonstrated a growth regulatory role for PGE2 in the glioblastoma multiforme cell line U87-MG. Unexpectedly, stimulation of U87-MG cells by PGE2 resulted in inhibition of the ERK 1/2 pathway. The present study was, therefore, undertaken to characterize PGE2-induced inhibition of ERK 1/2 and elucidate the underlying signaling mechanisms. We demonstrate that ERK 1/2 phosphorylation was transiently inhibited by PGE2 in a time-dependent manner. Dephosphorylation of ERK1/2 was detected at 5 min exposure to PGE2, reached maximum levels between 20-180 min and was sustained for 6 h. Levels of phosphorylated ERK 1/2 increased thereafter and at 24-48 h were higher than those found in unstimulated U87-MG cells. Raf-1 phosphorylation was also transiently inhibited by PGE2. Desphosphorylation of Raf-1 at Ser338 was detected at 10 min exposure to PGE2 and followed thereafter kinetics identical to those of ERK 1/2. Tyrosine kinase dependent- (EGF) and independent (TPA)-phosphorylation of ERK and Raf-1 were also attenuated by PGE2. PGE2-induced dephosphorylation of ERK1/2 and Raf-1 was detected in other glioma cell lines, including T98G, U118-MG, but not in primary astrocytes or brain endothelial cells. Other prostaglandins, including prostaglandin D2, had no effect on Raf-1 and ERK dephosphorylation. Pretreatment of U87-MG with okadaic acid (OA), an inhibitor of several Ser/Thr phosphatases, including PP2A, PP2B, PP1 and PP5, rescued Raf-1 and ERK dephosphorylation detected at 20 min exposure to PGE2, while an inactive analogue of OA had no effect. In contrast, fostriecin, a selective inhibitor of PP2A and PP1, failed to rescue PGE2-induced ERK 1/2 and Raf-1 dephosphorylation. Sodium orthovanadate, a tyrosine phosphatase inhibitor, had no effect on PGE2-induced ERK 1/2 dephosphorylation. RNai-mediated silencing of PP5, but not PP2A, and forced expression of the TPR domain of PP5, which acts as a dominant negative PP5 construct, partially rescued PGE2-induced Raf-1 and ERK-dephosphorylation. Taken together, these results demonstrate that PGE2 transiently dephosphorylates Raf-1 and ERK 1/2 via an okadaic acid-sensitive pathway involving activation of PP5. We speculate that transient inhibition of Raf-1 and ERK 1/2 activation by PGE2 could represent a mechanism by which glioma cells escape apoptosis caused by sustained activation of the ERK 1/2 pathway. (Supported by NIH Grant RO3 NS076765 to MTR).
Honokiol inhibits growth and migration of renal cell carcinoma

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ABSTRACT

Renal cell carcinoma (RCC) is a common urological cancer worldwide and is known to the high risk of recurrence and metastasis. Approximately 70% of patients with RCC will develop recurrence after surgical resection, and 25%-30% of patients will eventually develop progression to distant metastasis. Honokiol is a small-molecule polyphenol isolated from the genus Magnolia, which has been shown to be a potential anticancer agent in multiple facets of signal transduction. Here we demonstrate that honokiol inhibits proliferation of RCC cells 786-0 and A498 without affecting cell viability. Moreover, honokiol also significantly inhibited migration and invasion of 786-0 cells in a dose-dependent manner. DNA microarray analysis showed that honokiol regulated expression of many genes related to human tumor metastasis in 786-0 cells. Real time PCR analysis confirmed that the expression of metastasis suppressor KISS1 and its receptor, KISS1R, were upregulated in 786-0 cells after treatment with honokiol. In addition, the shape changes and excessive formation of actin stress fibers were identified in 786-0 cells treated with honokiol. This phenomenon disappeared when treated cells with the pharmacological Rho-kinase inhibitor Y-27632 and honokiol. This inhibition can also be identified in 786-0 cells treated with Y-27632 only. Our present results demonstrated that honokiol could inhibit the growth, migration and invasion of RCC, which is likely to be regulated by the Rho and Rho-Associated Kinase (ROCK) pathway. In conclusion, honokiol is a biologically active natural compound which can be considered for the alternative treatment of RCC. The investigation of detailed mechanisms and molecular targets are in progress.
Clinical Research Nurses in Methodist Research Institute

Jean M Nash, RN, BSN

Indiana University Health Methodist Research Institute

SUMMARY

The Clinical Research Group is comprised of 12 nurses who manage both the administrative and clinical aspects of pharmaceutical and device research trials. The clinical research nurses provide total hands on service from contract negotiation and IRB protocol submission to the enrollment of subjects, collection of data, and study close out. All Methodist Research Institute (MRI) nurses have their BSN degree and obtain their CCRC certification when eligible from the Association of Clinical Research Professionals (ACRP). The nurses provide clinical research support to the investigators at Methodist Hospital, North, and Saxony and foster the initiatives forged between IU Health and the Indiana University School of Medicine through studies with the IU Investigators. The group has been involved in over 70 studies in various phases of research in a number of areas.

The Clinical Research Group provides the following protocol management services:

- Assist with protocol and Informed Consent development
- Negotiate budget and legal contract with study sponsor
- Coordinate ancillary departments
- Educate caregivers on protocol requirements
- Submit device studies to CMS for pre-approval for billing
- Recruit, educate and follow up with patients
- Collect and document data
- Report adverse events to sponsor and IRB
- Communicate with investigators, sponsors, IRB & research subjects.
- Maintain financial oversight & review all billed services quarterly
- Provide 24-hour, 7 day-a-week accountability for all clinical trials at IU Health Methodist, North, and Saxony

IU Health Methodist Clinical Research Group

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