Third Annual Clinical Research Coordinator Research Excellence Award

The 3rd annual Research Excellence Award honors UTMC clinical research coordinators who exemplify excellence in knowledge, skills, and acumen of the research profession. The Jacobson Center for Clinical and Translational Research (JCCTR) established the award that was presented earlier this year to Chris Eisenhauer, RN, BSN, CCRC for her outstanding performance.

Chris has been working as a clinical research coordinator in the Department of Surgery for the last two years. Prior to this position she was a clinical research coordinator in Cardiology for seven years. Chris began her career at the former Medical College of Ohio in 2003.

"It is a privilege to work with the best doctors, doing what I love to do. The University of Toledo Medical Center has the most brilliant minds, and I get the opportunity to be a small part of the future by participating in research today. It is humbling to be recognized when we have so many amazing clinical research coordinators who do such a great job."

Both Dr. Nazzal and Dr. Schwann are Principal Investigators (PI's) involved with clinical trials research in the Department of Surgery.

Randomized Clinical Trials on Trial: Have They Lost Their Appeal?

Lance D. Dworkin, MD
Mercy Professor and Chair
Department of Medicine

Randomized, controlled trials (RCT) remain the gold standard of clinical trial design and generate the most reliable data on which to base clinical decision
contractions are rehabilitation programs that promote physical activity. We also know that intermittent ectopic ventricular contractions that are often observed in this setting. Years later, there is still no evidence that prolonged bed rest after an AMI is beneficial; instead we feel that exercise improves long term outcomes and refer patients to cardiac rehabilitation programs that promote physical activity. We also know that intermittent ectopic ventricular contractions are generally benign and that antiarrhythmic agents like lidocaine can actually improve power. Often a novel treatment is compared to the current standard of care but what should be done if the standard of care changes after the trial is underway? This is just a partial list of potential compromises that often determine the final protocol of any RCT. Given the inherent imperfections, every RCT can be criticized for any one of a number of reasons; the wrong population was enrolled, the wrong intervention was tested, the wrong endpoint was examined, the data are incomplete, and on and on. Accordingly, it is hardly surprising that single RCTs, no matter how well done, often fail to change clinical practice.

The biggest problem for many RCTs is enrollment. Potential subjects must agree to receive an experimental treatment that may very well be inferior to standard practice. They may be asked to remain in a trial for years, keeping extra office visits with unfamiliar providers and undergoing therapeutically irrelevant testing, all with little or no compensation. Concerned about loss of control and the unknown risks of the treatment being tested, physicians may be unwilling to refer their patients for inclusion. If a study fails to enroll adequate numbers of participants, then those that were enrolled have been exposed to risk with no potential for even a societal benefit. Even if enrollment is only delayed, the length of the study may need to be extended, increasing not only the cost but also the potential risks to the participants.

Understanding these issues, should large scale RCTs be abandoned and clinical decision making be based on observational data or cell culture or animal studies? In my view the history of medicine has answered this question through numerous examples where widely accepted, rational therapies supported by extensive preclinical and observational data were found to be useless or harmful when actually examined in a well-designed RCT.

Here is just one example from personal experience; there are many others. When I was a house officer, the standard treatment for an acute myocardial infarction (AMI) included prolonged bed rest in a quiet room and a continuous intravenous infusion of the antiarrhythmic, lidocaine, to suppress ectopic ventricle contractions that are often observed in this setting. Years later, there is still no evidence that prolonged bed rest after an AMI is beneficial; instead we feel that exercise improves long term outcomes and refer patients to cardiac rehabilitation programs that promote physical activity. We also know that intermittent ectopic ventricular contractions are generally benign and that antiarrhythmic agents like lidocaine can actually increase the risk of sudden death. Our current approach to patients with AMI including anticoagulation and early revascularization has reduced morbidity and mortality but was unknown at the time. All of these advances were tested and validated in large, prospective RCTs.

There are innovative approaches to clinical translational research that may help mitigate the time, cost, and complexity of traditional RCTs. A tremendous amount of clinical outcome data is now collected and housed in electronic medical records in medical centers and in practices around the world. In addition to the electronic medical record, claims data from national and private payers contains a wealth of clinical information, not only on costs, but also on treatments including drugs, devices, and procedures as well as clinically relevant outcomes such as ED visits, hospitalizations and readmissions. There is tremendous potential to tap these databases for clinical investigation, for example to compare the relative utility of different therapies. Novel statistical approaches and clinical trial designs are being developed and exploited, such as noninferiority trials that do not require a placebo group but can still provide evidence for the effectiveness of a novel therapy. Stratifying subjects based on genetic as well as clinical data may improve comparability and power, helping to
reduce the number of subjects that need to be studied. Nevertheless, although it is critically important to take full advantage of these novel approaches; I believe that for some questions, large, multicenter RCTs will always be needed.

Regardless of the setting in which we practice, I believe that all physicians should actively support clinical investigation, particularly for diseases where highly effective therapies are not available or where the relative efficacy of alternative approaches is unclear. This includes encouraging our patients to participate in clinical trials and to accept random assignment of therapy where there is equipoise between the alternatives. We should encourage government and Industry leaders, the NIH, and other funding agencies to continue to fund clinical research including large scale RCTs when necessary. We should avoid writing clinical practice guidelines that make specific treatment recommendations in the absence of good outcome data. This can have a chilling effect on our ability to conduct clinical research to gather the needed data. In situations where a clinical trial is not available, clinical outcome data should still be collected through registries or other databases to allow for eventual analysis. Regardless of the problem, every patient we treat creates both a clinical challenge and an opportunity to learn something useful. We owe it to our patients, to our profession, and to society not to waste these opportunities.

Clinical Research Snippets

Anand B. Mutgi, MD
Basil Akpunonu, MD

Hypertension is common and is estimated to affect 30% of the US population. It is associated with pathologic change in several end organs, but especially the brain (strokes), heart (various heart diseases as heart failure) and kidney (CKD and dialysis). Treatment of hypertension reduces these complications and related mortality. Major guidelines suggest a target blood pressure (BP) of < 140 / 90 mmHg in non-diabetic CKD and further reduction of < 130 / 80 mmHg for those with proteinuria. However, the optimal reduction in blood pressure and its benefit has been difficult, particularly in CKD. We reviewed the results of a meta-analysis addressing two different intensity blood pressure reduction strategies and its benefits on CKD and mortality.

Authors culled a total of 9 studies from review of the literature after applying specific exclusion criteria, ending with a total study population of 8,127 patients, followed for a median of 3.3 years. They compared studies with target BP of 140/90 mmHg or less to target BP of 130/80 mmHg or less in non-diabetic patients.

Mean change in GFR annually was not significant. Doubling of serum Creatinine and the number of patients reaching end stage kidney disease was not statistically different (RR, 0.99; 95% CI, 0.76-1.29). Similarly, all-cause mortality was not different. However, a further subgroup analysis showed possible benefit of intense BP reduction in non-black patients and those with significant proteinuria at the onset. There was not enough data to address the effect on the black population.

This was a timely and well done meta-analysis of data to address the effect of intensity of BP lowering on kidney disease and mortality. The results of the meta-analysis is in step with our current understanding that BP reduction to below 140/90 mmHg in non-diabetic patients does not prevent kidney disease progression over a 3 year period and is currently not indicated. However, this study does not address its impact on cardiac and cerebrovascular events.

Clinical Research Snippets
Sadik A. Khuder, PhD
Anand B. Mutgi, MD

Lack of physical activity has been shown to be associated with increased risk of cardiovascular disease (CVD) and many other chronic conditions: There is an overwhelming evidence that regular physical activity has important and wide-ranging health benefits. Regular participation in physical activity has been suggested to control weight, cholesterol concentration, and blood pressure. However, little is known about the benefits of isolated or low frequency of physical activity. The present study examined the associations between different patterns of physical activity and mortality.

The authors analyzed data derived from the Health Survey for England (HSE) and Scottish Health Survey (SHS) from 1994 to 2012 and included 63,591 survey respondents. Of these, 62.8% were classified as inactive (not reporting any moderate- or vigorous-intensity physical activities); 22.4%, as insufficiently active (reporting less than 150 min/wk in moderate-intensity physical activity and less than 75 min/wk in vigorous-intensity physical activity); 3.7%, as weekend warriors (reporting at least 150 min/wk in moderate-intensity physical activity or at least 75 min/wk in vigorous-intensity physical activity from 1 or 2 sessions); and 11.1%, as regularly active (reporting at least 150 min/wk in moderate-intensity physical activity or at least 75 min/wk in vigorous-intensity physical activity from 3 or more sessions).

Compared with the inactive participants, all-cause mortality was reduced by 31% in the insufficiently active participants, 30% in the weekend warrior participants, and 35% in the regularly active participants. The CVD mortality was reduced by 37% in the insufficiently active participants, 40% in the weekend warrior participants, and 41% in the regularly active participants.

The cancer mortality was reduced by 14% in the insufficiently active participants, 18% in the weekend warrior participants, and 21% in the regularly active participants.

The findings of this study suggest that some sessions of isolated physical activity or low activity is better than no activity for reducing mortality risk. Those who exercise 1 to 2 times per week may lower their risk even further with more frequent activity. A condensed pattern of physical activity may be sufficient to reduce all-cause, CVD, and cancer mortality.

Clinical Research Snippets

Andrew M. Jurgenson, PA-C, MSBS
Basil E. Akpunonu, MD

Clostridium difficile infection (CDI) incidence has doubled over the past ten years and poses a significant cost burden estimated at $4.8 billion dollars. Risk factors for CDI include antibiotic usage, increased age and hospitalization with latter carrying the greatest risk. Despite previous systematic reviews demonstrating the efficacy of probiotics in reducing CDI incidence in hospitalized adults, the American College of Gastroenterology and the Society for Healthcare Epidemiology of America guidelines do not recommend probiotics for primary prevention of CDI. The lack of recommendation is likely attributable to the PLACIDE study that demonstrated no evidence for primary prevention of CDI with probiotics. We reviewed a recently released systematic review demonstrating the timely use of probiotics and the subsequent reduction in CDI.
www.sciencedirect.com

Authors analyzed data from a total of 19 published studies from multiple literature search excluding subjects who were pregnant, immunocompromised, requiring intensive care, had a prosthetic heart valve, or had a pre-existing gastrointestinal disorder. The study included 6,261 subjects randomized either to a probiotic or placebo group. The primary and secondary outcomes include incidence of CDI and adverse events. Furthermore, secondary analyses investigated the effects of probiotic species, dose, timing, formulation, duration and study quality.

The incidence of CDI in the probiotic cohort was 1.6%; which was significantly lower than the CDI incidence of the control cohort, 3.9%. Furthermore, the pooled relative risk in the probiotic group was 0.42 (95% CI, 0.30 – 0.57). Interestingly, the meta-regression analysis indicated that the efficacy of probiotics was significantly greater if they were administered closer to the initiation of antibiotics and especially if administered within the first two days following initiation of antibiotics (RR, 0.32, 95% CI, 0.22-0.48). There was also a significant decline in efficacy associated with each day delay in starting probiotics. Subjects administered probiotics did not demonstrate any increased risk in adverse outcomes.

This study contradicts the previous PLACIDE trial and also indicated that the timely use of probiotics correlates with a significant reduction in hospital acquired CDI in adults. The discrepancy in data between this study and the previous PLACIDE trial is likely attributable to the failure to assess CDI in 40% of hospitalized patients with diarrhea as well as late initiation of probiotics up to seven days following antibiotic administration. There is promising evidence that probiotic formulations with Lactobacillus and Lactobacillus in combination with either Streptococcus or both Streptococcus and Bifidobacterium are effective. However, there is no statistically significant evidence to suggest a differential beneficial effect favoring one combination. This study suggests that probiotic administration within two days of antibiotic initiation reduce the risk of CDI by over 50% in hospitalized adults, with no increase in adverse events. By implementing these findings into clinical practice, it is estimated that the potential health care cost savings could approach $500 million dollars annually.

New Clinical Trials

Dr. Mohamed - Medicine

S1418/BR006 A Randomized Phase III Trial to Evaluate the Efficacy and Safety of MK-3475 (Pembrolizumab) as Adjuvant Therapy for Triple Receptor-Negative Breast Cancer with ≥ 1 cm Residual Invasive Cancer or Positive Lymph Nodes (ypN+) after Neoadjuvant Chemotherapy.
Dr. Mohamed - Medicine

A011401: Randomized Phase III Trial Evaluating the Role Of Weight Loss in Adjuvant Treatment of Overweight and Obese Women with Early Breast Cancer
Dr. Mohamed - Medicine

M13-813: A Randomized, Placebo Controlled Phase 2b/3 Study of ABT-414 with Concurrent Chemoradiation and Adjuvant Temozolomide in Subjects with Newly Diagnosed Glioblastoma (GBM) with Epidermal Growth Factor Receptor (EGFR) Amplification (Intellance 1)
Dr. Krishna Reddy - Radiation Oncology

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