

# Thalidomide-Associated Deep Vein Thrombosis and Pulmonary Embolism

BENNETT CL, SCHUMOCK GT, DESAI AA, KWAAN HC, RAISCH DW,  
NEWLIN R, STADLER W

**Abstract:** Thalidomide has become an important drug in the treatment of cancer. Although most physicians are aware of side effects associated with fetal development, other side effects may also be important, especially since the use of the drug has expanded. This manuscript

describes the occurrence of pulmonary embolism associated with the use of thalidomide. Since this side effect is often fatal, it is important for physicians to monitor patients for clotting abnormalities during treatment.

*(Am J Med 113:603-606, 2002)*  
*CSP CRPCC Albuquerque, NM*

## Pharmacoeconomic Implications of Large Multi-Center Clinical Trials

RAISCH DW, NETRAVALI SS, HARRIS CL

**Abstract:** Large multi-center clinical trials often have important economic implications. However, interpreting and applying these findings in practice may be difficult. This editorial identifies the advantages and disadvantages of performing pharmacoeconomic analyses of large multi-center clinical trials.

Some of the important issues are whether or not the trial patients are similar to those in practice due to trial design, how differences in the treatment of international patients affect the results, and whether the results can be considered to represent a class effect.

*(Ann Pharmacother 37:447-50, 2003)*  
*CSP CRPCC Albuquerque, NM*

# Economic Comparison of Home-Care Based Versus Hospital-Based Treatment of Chemotherapy-Induced Febrile Neutropenia in Children

RAISCH DW, HOLDSWORTH MT, WINTER SS, HUTTER JJ, GRAHAM ML

**Abstract:** *Objective:* The purpose of this study was to compare health-care resource utilization and outcomes among children treated for low-risk febrile neutropenia (FN) in a hospital-based setting with those treated in a home-care-based setting.

*Methods:* The perspective of this retrospective, cohort study was the health payer. We collected health-care utilization and treatment outcome data from medical records of 63 children (26 boys and 37 girls) with low-risk, chemotherapy-induced FN who were treated at the University of Arizona (27 children, the hospital-based group) and University of New Mexico (36 children, the home-care-based group). We identified 144 FN episodes (72 episodes in each group). Health-care utilization included physician visits, home-care visits, laboratory visits, outpatient visits, hospital days, intensive care unit days, medical tests and studies, and medications used to manage FN (e.g., filgrastim, antimicrobials, and ancillary drugs and supplies). We applied uniform charges, based on those used at the University of New Mexico in 1998. We collected outcomes of the FN treatment (success vs. failure and time to resolution, defined as number of days of antibiotic therapy). Rates of positive blood cultures during treatment were also compared. Data were analyzed using nonparametric Mann-Whitney U tests

for continuous data and chi-square analysis for categorical data. Sensitivity analyses were conducted by varying the amount of total resource utilization, as well as utilization of specific health-care resources.

*Results:* There was no difference in outcome; all episodes of treatment in both groups resulted in successful recovery from FN. Time to resolution of FN was 8.3 +/- 2.7 days for home-care FN episodes versus 7.3 +/- 3.6 days for hospital FN episodes ( $P = .064$ ). Median charge per FN episode was significantly ( $P < .001$ ) greater when managed in the hospital compared to home care (9392 US dollars vs. 5893 US dollars). There was greater use of laboratory and radiographic studies in the hospital-based patients ( $P < .01$ ). However, children in the home-care-based group were more often treated with granulocyte colony-stimulating factor (filgrastim, median charge 1085 US dollars vs. 451 US dollars,  $P < .001$ ), and median antibiotic charges were higher (2523 US dollars vs. 1526 US dollars,  $P < .001$ ). Positive blood cultures were more common among the hospital-based FN treatments (30.6 vs. 11.1%,  $P = .012$ ).

*Conclusions:* We found that management of low-risk FN in a home-care-based setting was associated with significantly lower median total charges with no differences in outcome.

(*Value Health* 6:158-166, 2003)  
CSP CRPCC Albuquerque, NM

# Pain and Distress from Bone Marrow Aspirations and Lumbar Punctures

HOLDSWORTH MT, RAISCH DW, WINTER SS, FROST JD, MORO MA, DORAN NH,  
PHILLIPS J, PANKEY JM, MATHEW P

**Abstract:** *Objective:* To compare the efficacy of 3 different pharmacologic regimens to relieve pain and distress in children with cancer undergoing bone marrow aspirations (BMAs) and lumbar punctures (LPs).

*Design:* Retrospective cohort study with crossovers for some patients.

*Patients And Methods:* The pain and distress ratings of patients undergoing BMAs (n = 73) and LPs (n = 105) were examined in a comparison of 3 different interventions: (1) a topical eutectic mixture of lidocaine and prilocaine (EMLA cream), (2) oral midazolam and EMLA cream, or (3) propofol/fentanyl general anesthesia. The choice of the intervention depended on patient/parent request. A validated faces pain scale was completed by the child or parent following each BMA or LP. The faces pain scale includes ratings of the severity of pain (from 0 = none to 5 = severe) and ratings of how frightened (from 0 = not scared to 5 = scared) the child was prior to each procedure. Comparisons of the pain and distress ratings were made among all patients for their first procedure and also within individual patients who had received >1 of the

3 interventions. Independent comparisons between the first treatments received by each patient were analyzed using Kruskal-Wallis tests. Comparisons of different crossover treatments received by individual patients were analyzed using Wilcoxon tests. **RESULTS:** For all first procedures, mean +/- SD pain and distress ratings during LPs were significantly lower when propofol/fentanyl was used (n = 43; 0.4 +/- 1.0 and 1.4 +/- 1.7) versus either EMLA (n = 29; 2.4 +/- 1.7 and 2.9 +/- 1.9) or midazolam/EMLA (n = 33; 2.4 +/- 1.8 and 2.7 +/- 1.8), respectively. Pain and distress ratings during BMAs were also significantly lower with propofol/fentanyl (n = 29; 0.5 +/- 1.0 and 1.2 +/- 1.7) versus EMLA (n = 21; 3.5 +/- 1.6 and 3.3 +/- 1.8) or midazolam/EMLA (n = 23; 3.3 +/- 1.5 and 3.0 +/- 1.9), respectively. When data were analyzed within each patient, these differences were also present.

*Conclusions:* Children receiving propofol/fentanyl general anesthesia experienced significantly less procedure-related pain and distress than did those receiving either EMLA or oral midazolam/EMLA.

(*Ann Pharmacother* 37:17-22, 2003)  
CSP CRPCC Albuquerque, NM

# Incidence and Impact of Adverse Drug Events in Pediatric Patients

HOLDSWARTH MT, FICHTL RE, BEHTA M, RAISCH DW, MENDEZ-RICO E, ADAMS A, GREIFER M, BOSTWICK S, GREENWALD BM

**Abstract: Objectives:** To determine the incidence and causes of adverse drug events (ADEs) and potential ADEs in hospitalized children, and to examine the consequences of these events.

**Design:** Prospective review of medical records and staff interviews were performed. The ADEs were defined as injuries from medications or lack of an intended medication, and potential ADEs, as errors with the potential to result in injury.

**Setting:** A general pediatric unit and a pediatric intensive care unit in a metropolitan medical center.

**Patients:** A total of 1197 consecutive patient admissions were studied from September 15, 2000, to May 10, 2001. The admissions represented a total of 922 patients and 10,164 patient-days. **RESULTS:** The ADEs (6/100 admissions, 7.5/1000 patient-days) and potential ADEs (8/100 admissions, 9.3/1000 patient-days) were common in hospitalized children. Demographic

variables associated with the occurrence of these events were the length of hospital stay, case-mix index, and amount of medication exposure. After adjusting for length of stay, medication exposure continued to have a significant influence on ADEs and potential ADEs. For ADEs, 18 (24%) were judged to be serious or life threatening. Most ADEs were not associated with major or permanent disability. Patients with both ADEs and potential ADEs were less likely to be routinely discharged and more likely to be discharged with home health care or to another institution, suggesting that patient disposition was not related to the adverse event.

**Conclusions:** Both ADEs and potential ADEs are common among hospitalized children with greater disease burden and medication exposure. These findings suggest that these events were a consequence, rather than a cause, of more severe illness.

(Arch Pediatr Adolesc Med 157:60-65, 2003)  
CSP CRPCC, Albuquerque, NM

# Promoting Good Clinical Practices in the Conduct of Clinical Trials: Experiences in the Department of Veterans Affairs Cooperative Studies Program

SATHER MR, RAISCH DW, HAAKENSON CL, BUCKELEW JM, FEUSSNER JR

**Abstract:** The ever-increasing concern for the welfare of volunteers participating in clinical trials and for the integrity of the data derived from those trials has generated the concept of Good Clinical Practice (GCP). The Veterans Affairs Cooperative Studies Program, in anticipation of the need to comply with GCP guidelines, developed a Site Monitoring and Review Team (SMART), which consist of a Good Clinical Practice Monitoring Group and a Good Clinical Practice Review Group. The review group conducted 335 site reviews from fiscal years (FY) 1999 through 2001 to assess and encourage adherence to GCP. Data from reviews were compared for two time periods, a 2-year implementation period (FYs 1999/2000, n = 204) and a continuing follow-up period (FY 2001, n = 131). Overall, high GCP adherence was exhibited by 11.3% (n = 23) of study sites in FY 1999/2000 versus 20.6% (n = 27) in FY 2001, average to good adherence was exhibited by 84.3% (n =172) in FY 1999/2000 versus 77.0% (n = 101) in FY 2001, and below average adherence was

exhibited by 4.4% (n = 9) versus 1.5% (n = 3) in these two periods. These changes were statistically significant by chi square analysis (p = 0.029). Moreover, GCP adherence was assessed within eight GCP focus areas: patient informed consent, protocol adherence, safety monitoring, institutional review board interactions, regulatory document management, patient records in investigator file, drug/device accountability, and general site operations. Median assessment scores for all 62 GCP review elements improved from 0.82 to 0.89 (p < 0.001). Median assessment scores for the 14 selected critical GCP items improved from 0.78 to 0.89 (p < 0.001). Median scores for five of the eight GCP focus areas improved significantly (p<0.001) between the two time periods. These data suggest that the site-oriented activities of SMART combined with centralized quality assurance activities of the coordinating centers represent an integrated, versatile program to promote and assure GCP adherence and data integrity in Cooperative Studies Program trials.

*(Control Clin Trials 24:570-84, 2003)*  
*CSP CRPCC Albuquerque, NM*

## Dissemination of Information on Potentially Fatal Adverse Drug Reactions for Cancer Drugs from 2000-2002: First Results from the Research on Adverse Drug Events and Reports Projects

LADIEWSKI LA, BELKNAP SM, NEBEKER JR, SARTOR O, LYONS EA, KUZEL TC, TALLMAN MS, RAISCH DW, AUERBACH AR, SCHUMOCK GT, KWAAN HC, BENNETT CL

**Abstract: Purpose:** To describe the clinical findings, occurrence rates, causality evidence, and dissemination media for serious cancer drug-associated adverse drug reactions (ADRs) reported in the postmarketing setting.

**Methods:** ADRs were termed serious if they resulted in death or severe organ failure. ADR information for oncology drugs from package insert (PI) revisions, so-called Dear Doctor letters, and journal articles was evaluated to identify serious ADRs reported from 2000 to 2002. Timing and content of information disseminated was assessed.

**Results:** Twenty-five serious ADRs associated with 22 oncology drugs were identified after approval. Approximately half of these serious ADRs are associated with drugs approved before 1995. ADRs were

described in articles in medical journals (17 ADRs), PI revisions (18 ADRs), and Dear Doctor letters (12 ADRs). PI revisions occurred less than 1 year after peer-reviewed publication for four ADRs. These revisions often differed for similar ADRs that occurred with drugs of the same class. Five of the seven ADRs lacking PI changes occurred with off-label use, for which PI change is not recommended by US Food and Drug Administration (FDA) policy. No cancer drug was withdrawn from the market during the observation period.

**Conclusion:** Our findings demonstrate that serious ADRs may be discovered as long as 36 years after a drug receives FDA approval. This suggests a need for continued vigilance and efficient strategies for dissemination of information about ADRs associated with cancer drugs.

*(J Clin Oncol 21:3859-3866, 2003)  
CSP CRPCC Albuquerque, NM*

# Impact of Pharmacists' Directive Guidance Behaviors on Patient Satisfaction

SINGHAL PK, GUPCHUP GV, RAISCH DW, SCHOMER JC, HOLDWORTH MT

**Abstract:** *Objective:* To determine the impact of directive guidance (DG) behaviors by pharmacists on patient satisfaction with pharmaceutical care services. DG behaviors are social support behaviors and include such activities as supplying information about medications and providing encouragement and feedback regarding drug therapy.

*Design:* Cross-sectional observational study using a self-administered survey. **SETTING:** Two university-affiliated ambulatory care clinics, two chain pharmacies, and one independent pharmacy.

*Patients:* One hundred sixty patients with a chronic disease (e.g., asthma, hypertension, diabetes).

*Main Outcome Measure:* Patient satisfaction with pharmaceutical care services.

*Results:* A total of 160 completed questionnaires were collected from patients at 5 sites. Overall, patients patronizing ambulatory care clinics perceived higher rates of DG behaviors and were more satisfied with pharmaceutical care services, compared with patients in community pharmacies ( $P < .05$ ). The hierarchical regression model was significant ( $F(13,112) = 4.9091$ ,  $P < .001$ ). DG behaviors explained 32.4% ( $P < .001$ ) of the variance in patient satisfaction with pharmaceutical care services.

*Conclusion:* Higher rates of DG behaviors by pharmacists are associated with greater patient satisfaction with pharmaceutical care services.

(*J Am Pharm Assoc (Wash)* 42: 407-412, 2002)  
CSP CRPCC Albuquerque, NM

# Opioid Dependence Treatment, Including Buprenorphine/Naloxone

RAISCH DW, FYE CL, BOARDMAN KD, SATHER MR

**Abstract:** *Objective:* To review opioid dependence (OD) and its treatment. Pharmacologic treatments, including the use of buprenorphine/naloxone, are presented. Pharmaceutical care functions for outpatient OD treatment are discussed.

*Data Sources:* Primary and review articles were identified by MEDLINE and HEALTHSTAR searches (from 1966 to November 2000) and through secondary sources. Tertiary sources were also reviewed regarding general concepts of OD and its treatment.

*Study Selection/Data Extraction:* Relevant articles were reviewed after identification from published abstracts. Articles were selected based on the objectives for this article. Studies of the treatment of OD with buprenorphine were selected based on the topic (pharmacology, pharmacokinetics, adverse reactions) and study design (randomized, controlled clinical trials in patients with OD with active/placebo comparisons and/or comparisons of active OD treatments). Articles regarding pharmacists' activities in the treatment and prevention of OD were reviewed for the pharmaceutical care section.

*Data Synthesis:* OD is considered a medical disorder with costly adverse health outcomes. Although methadone maintenance treatment (MMT) is cost-effective for OD, only about 12% of individuals with OD

receive this treatment. Psychological and pharmacologic modalities are used to treat OD, but patients often relapse. Drug therapy includes alpha 2-agonists for withdrawal symptoms, detoxification regimens with or without opioids, opioid antagonists, and opioid replacement including methadone, levomethadyl acetate, and buprenorphine. The Drug Addiction Treatment Act of 1999 allows for office-based opioid replacement therapies. Sublingual buprenorphine with naloxone can be used in this milieu. Buprenorphine with naloxone is currently under new drug application review with the Food and Drug Administration. Clinical research shows buprenorphine to be equal in effectiveness to methadone, but safer in overdose due to its ceiling effect on respiratory depression. It has lower abuse potential and fewer withdrawal symptoms when discontinued. Naloxone is included to decrease diversion and injection of the tablets. Pharmacists in outpatient settings who are familiar with OD have opportunities to provide pharmaceutical care to patients receiving this treatment. Pharmaceutical care functions for OD include ensuring appropriate drug administration, monitoring adverse effects, alleviating withdrawal symptoms, treating intercurrent illnesses, minimizing diversion, and preventing relapse.

*Conclusions:* OD is a critical unmet health problem in the US.

**Opioid Dependence Treatment, Including Buprenorphine/Naloxone**

Buprenorphine combined with naloxone represents an innovative treatment for OD in outpatient

settings. This new treatment has advantages over MMT.

*(Ann Pharmacother 36(2):312-321, 2002)*  
*CSP CRPCC Albuquerque, NM*

**Pneumonitis Associated with Nonsteroid  
Antiandrogens: Presumptive Evidence of a Class Effect**

BENNETT CL, RAISCH DW, SARTOR O

**Abstract:** This manuscript compares nonsteroidal anti-androgens in regards to development of pneumonitis. Through evaluating the MedWatch reports from the Food and Drug Administration regarding these agents we characterized the signs and symptoms and patient

demographics of pneumonitis among patients treated with anti-androgens. We found that although certain agents had more reports of pneumonitis, the adverse event was reported for all drugs within the class.

*(Ann Intern Med 137:625, 2002)*  
*CSP CRPCC Albuquerque, NM*

# Clonidogrel-Associated TTP. An Update of Pharmacovigilance Efforts Conducted by Independent Researchers, Pharmaceutical Suppliers, and the Food and Drug Administration

ZAKARIJA A, BANDARENKO N, PANDEY DK, AUERBACH A, RAISCH DW, KIM B, KWAAN HC, MCKOY JM, SCHMITT BP, DAVIDSON CJ, YARNOLD PR, GORELICK PB, BENNETT CL

**Abstract:** *Background and Purpose:*

Since the 1999 identification of clonidogrel-associated thrombotic thrombocytopenic purpura (TTP) through independent active surveillance, subsequent cases have been identified by pharmaceutical suppliers of clonidogrel and the Food and Drug Administration (FDA). For cases of clonidogrel-associated TTP reported between 1998 to 2002, we evaluated the quality and timeliness of data from 3 reporting systems--independent active surveillance (n=13), pharmaceutical suppliers (n=24), and the FDA (n=13)--and identified prognostic factors associated with mortality.

*Methods:* This study assessed the completeness of information on TTP diagnosis, treatment response, and causality from the 3 reporting systems. In addition, predictors of mortality were identified through classification tree analysis.

*Results:* Completeness, timeliness, and certainty of diagnosis were best for cases obtained by active surveillance, intermediate for cases reported to the pharmaceutical supplier, and poorest for cases reported directly to the FDA. Clonidogrel had been used for  $\leq 2$  weeks by 65%. The survival rate for patients with clonidogrel-associated TTP was 71.2%. Receipt of therapeutic plasma exchange within 3 days of onset of TTP increased the likelihood of survival (100% versus 27.3%,  $P < 0.001$ ).

*Conclusions:* Compared with reports submitted by suppliers or the FDA, reports obtained through active surveillance provided timelier and more complete information. Clonidogrel-associated TTP often occurs within 2 weeks of drug initiation, occasionally relapses, and has a high mortality if not treated promptly.

(*Stroke* 35: 533-537, 2004)  
CSP CRPCC Albuquerque, NM

# Low Protein Diet Mediated Renoprotection in Remnant Kidneys: Renal Autoregulatory Versus Hypertrophic Mechanisms

KAREN A GRIFFIN, MARIA PICKEN, ANITA GIOBBIE-HURDER, AND ANIL K BIDANI

**Abstract:** *Background:* The mechanism of low protein diet conferred renoprotection in the ablation model remains controversial. Blockade of glomerular hypertrophy, reduced preglomerular vasodilation, and preserved autoregulation have all been postulated. The potential differential impact of calcium channel blockers on these mechanisms and glomerulosclerosis was examined.

*Methods:* Rats with 5/6 renal ablation received either a 25% standard protein diet, an 8% low protein diet and a low protein diet with either verapamil or amlodipine. Renal autoregulatory and morphometric studies were performed at 3 weeks before the development of significant injury, and the assessment of glomerulo-

sclerosis after 7 weeks of continuous blood pressure radiotelemetry in additional rats.

*Results:* The preserved renal autoregulation in low protein rats was abolished by both calcium channel blockers, with the impairment being either comparable to (low protein + verapamil) or greater than the standard protein rats (low protein + amlodipine). Neither calcium channel blocker blocked the inhibitory effects of low protein diet on renal blood flow, kidney weight, and glomerular volume.

*Conclusions:* Preservation of renal autoregulation and not inhibition of hypertrophy is the critical component in low protein diet-conferred glomeruloprotection.

(*Kidney Int* 63 (2):607-616,2003)  
CSPCC Hines, IL

# Long-term Follow-up of the CAD/CAM Patient Fitted Total Temporomandibular Joint Reconstruction System

LOUIS F MERCURI, DDS, MS, LARRY M WOLFORD, DDS, BRUCE SANDERS, DDS,  
R DEAN WHITE, DDS, MS, ANITA GIOBBIE-HURDER, MS

**Abstract:** *Purpose:* The purpose of this study was the assessment of the long-term safety and effectiveness of the Techmedica (Camarillo, CA) CAD/CAM Total Temporomandibular Joint Reconstruction System (now called the TMJ Concepts Patient Fitted Total Temporomandibular Joint Reconstruction System, Ventura, CA).

*Patients and Methods:* A survey was mailed to the available addresses of 170 (79%) of the 215 patients who had been implanted with the Techmedica System devices between 1990 and 1994. Seventy-nine (46%) surveys were returned by the US Postal Service as undeliverable. Three patients (1.4%) were reported as deceased in returns from relatives. Therefore, of the remaining 91 possible responses, 60 (65.9%) were returned. Fifty-eight surveys, considered complete and valid (96.7%), representing 97 (39 bilateral, 19 unilateral) devices with a mean follow-up of  $107.4 \pm 15.5$  months (range, 60 to 120 months) were analyzed. Subjective data related to pain, mandibular function, diet consistency, and present quality

of life were collected using visual analog scales. Objective measures of mandibular interincisal opening and lateral excursions were obtained from direct measurements using the Therabite (Therabite, Philadelphia, PA) measuring scale provided in the survey with instructions as to its use.

*Results:* Analysis of the subjective data at 10 years revealed a 75% reduction in mean pain scores and a 68% increase in mean mandibular function and diet consistency scores ( $P < .0001$ ). Analysis of objective data revealed a 30% improvement in mandibular range of motion after 10 years ( $P = .0009$ ). Long-term quality of life improvement scores were statistically related to the number of prior temporomandibular joint operations the patients had undergone.

*Conclusion:* These data indicate that the CAD/CAM Patient Fitted Total Temporomandibular Joint Reconstruction System has proved to be a safe and effective long-term management modality in the patient population surveyed for this study.

(*J Oral Maxillofac Surg* 60:1440-1448, 2002)  
CSPCC Hines, IL

# A Primer and Comparative Review of Major U.S. Mortality Databases

DIANE C COWPER, MA, JOSEPH D KUBAL, MA, CHARLES MAYNARD, PHD,  
DENISE M HYNES, PHD, RN

**Abstract:** *Purpose:* Mortality data are important tools for research requiring vital status information. We reviewed the major mortality databases and mortality ascertainment services available in the United States, including the National Death Index (NDI), the Social Security Administration (SSA) files, and the Department of Veterans Affairs databases.

*Methods:* The content, reliability, and accuracy of mortality sources are described and compared. We also describe how investigators can gain access to these resources and provide further contact information.

*Results:* We reviewed the accuracy of major mortality sources. The sensitivity (i.e., the proportion of the true number of deaths) of the

NDI ranged from 87.0% to 97.9%, whereas the sensitivity for the VA Beneficiary Identification and Records Locator System (BIRLS) ranged between 80.0% and 94.5%. The sensitivity of SSA files ranged between 83.0% and 83.6%. Sensitivity for the VA Patient Treatment Files (PTF) was 33%.

*Conclusions:* While several national mortality ascertainment services are available for vital status (i.e., death) analyses, the NDI information demonstrated the highest sensitivity and, currently, it is the only source at the national level with a cause of death field useful for research purposes. Researchers must consider methods used to ascertain vital status as well as the quality of the information in mortality databases.

(*Ann Epidemiol* 12:462-468, 2002)  
CSPCC Hines, IL

# Modeling Clustered Count Data with Excess Zeros in Health Care Outcomes Research

KWAN HUR, DONALD HEDEKER, WILLIAM HENDERSON, SHUKRI KHURI, JENNIFER DALEY

**Abstract:** In health research, count outcomes are fairly common and often these counts have a large number of zeros. In order to adjust for these extra zero counts, various modifications of the Poisson regression model have been proposed. Lambert (Lambert, D., *Technometrics* 34: 1-14, 1992) described a zero-inflated Poisson (ZIP) model that is based on a mixture of a binary distribution ( $\pi_i$ ) degenerated at zero with a Poisson distribution ( $\delta_i$ ). Depending on the relationship between  $\pi_i$  and  $\delta_i$ , she described two variants: a ZIP and a ZIP ( $t$ ) model. In this paper, we extend these models for the case of

clustered data (e.g., patients observed within hospitals) and describe random-effects ZIP and ZIP ( $t$ ) models. These models are appropriate for the analysis of clustered extra-zero Poisson count data. The distribution of the random effects is assumed to be normal and a maximum marginal likelihood estimation method is used to estimate the model parameters. We applied these models to data from patients who underwent colon operations from 123 Veterans Affairs Medical Centers in the National VA Surgical Quality Improvement Program.

*(Health Services & Outcomes Research Methodology 3: 5-20, 2002)*  
CSPCC Hines, IL

# The National Surgical Quality Improvement Program in Non-Veterans Administration Hospitals Initial Demonstration of Feasibility

AARON S FINK, MD, DARRELL A CAMPBELL, JR, MD, ROBERT M MENTZER, JR, MD,  
WILLIAM G HENDERSON, PHD, JENNIFER DALEY, MD, JANET BANNISTER, RN,  
KWAN HUR, PHD, SHUKRI F KHURI, MD

**Abstract:** *Objective:* To assess the feasibility of implementing the National Surgical Quality Improvement Program (NSQIP) methodology in non-VA hospitals.

*Summary Background Data:* Using data adjusted for patient preoperative risk, the NSQIP compares the performance of all VA hospitals performing major surgery and anonymously compares these hospitals using the ratio of observed to expected adverse events. These results are provided to each hospital and used to identify areas for improvement. Since the NSQIP's inception in 1994, the VA has reported consistent improvements in all surgery performance measures. Given the success of the NSQIP within the VA, as well as the lack of a comparable system in non-VA hospitals, this pilot study was undertaken to test the applicability of the NSQIP models and methodology in the nonfederal sector.

*Methods:* Beginning in 1999, three academic medical centers volunteered the time of a dedicated surgical nurse reviewer who was trained in NSQIP methodology. At each academic center, these nurse reviewers used NSQIP protocols to abstract clinical data from general surgery and vascular surgery patients. Data were manually collected and then transmitted via the Internet to a secure web site

developed by the NSQIP. These data were compared to the data for general and vascular surgery patients collected during a concurrent time period (10/99 to 9/00) within the VA by the NSQIP. Logistic regression models were developed for both non-VA and VA hospital data. To assess the models' predictive values, C-indices (0.5 = no prediction; 1.0 = perfect prediction) were calculated after applying the models to the non-VA as well as the VA databases.

*Results:* Data from 2,747 (general surgery 2,251; vascular surgery 496) non-VA hospital cases were compared to data from 41,360 (general surgery 31,393; vascular surgery 9,967) VA cases. The bivariate relationships between individual risk factors and 30-day mortality or morbidity were similar in the non-VA and VA patient populations for over 66% of the risk variables. C-indices of 0.942 (general surgery), 0.915 (vascular surgery), and 0.934 (general plus vascular surgery) were obtained following application of the VA NSQIP mortality model to the non-VA patient data. Lower C-indices (0.778, general surgery; 0.638, vascular surgery; 0.760, general plus vascular surgery) were obtained following application of the VA NSQIP morbidity model to the non-VA patient data. Although the non-

VA sample size was smaller than the VA, preliminary analysis suggested no differences in risk-adjusted mortality between the non-VA and VA cohorts.

*Conclusions:* With some adjustments, the NSQIP methodology can be implemented and generates reasonable predictive models within non-VA hospitals.

(*Ann Surg* 236 (3): 344-354, 2002)  
CSPCC Hines, IL

## The Impact of Hepatitis C Status on Postoperative Outcome

RAMSEY C CHEUNG, MD, FRANK HSIEH, PH D, YAJIE WANG, MS,  
AND JOHN B. POLLARD, MD

**Abstract:** The impact of the hepatitis C virus (HCV) infection on the postoperative complication rate is unknown. We identified a population of surgical patients ( $n = 2457$ ) for whom the HCV antibody (anti-HCV) had been measured and compared after surgical complications and mortality between those who were positive (17.9%) versus negative. The complication rates were 10% in the anti-HCV positive and 13% in the negative group ( $P = 0.125$ ), whereas the mortality rates were 0.7% and 2.5%, respectively ( $P = 0.017$ ). The anti-HCV positive patients were younger, had lower ASA physical status, and underwent shorter procedures. In the univariate analysis, emergent surgery and high ASA physical status but not anti-HCV positivity were associated with a more frequent complication. In the multivariate analysis, the urgency of surgery, age, ASA physical status,

length of surgery, and preoperative hematocrit (but not platelet count) were associated with complications. Anti-HCV positivity was associated with an odds ratio for having a complication of 1.08 (95% confidence interval, 0.90–1.30), which was not statistically significant ( $P = 0.405$ ). In conclusion, we were unable to show HCV antibody status to be an independent risk factor for postoperative complications when other co-factors were considered.

**Implications:** In this large study at a Veterans Administration medical center, the urgency of surgery, age, ASA physical status, length of surgery, and preoperative hematocrit were all independently associated with postoperative complications. However, hepatitis C infection was not an independent risk factor for postoperative complications.

(*Anesth Analg* 97:550-4, 2003)  
CSPCC Palo Alto, CA

# An Overview of Variance Inflation Factors for Sample-Size Calculation

FY HSIEH, PW LAVORI, HJ COHEN, AND JR FEUSSNER

**Abstract:** For power and sample-size calculations, most practicing researchers rely on power and sample-size software programs to design their studies. There are many factors that affect the statistical power that, in many situations, go beyond the coverage of commercial software programs. Factors commonly known as design effects influence statistical power by inflating the variance of the test statistics. The authors quantify how these factors affect the variances so that researchers can adjust the statistical

power or sample size accordingly. The authors review design effects for factorial design, crossover design, cluster randomization, unequal sample-size design, multiarm design, logistic regression, Cox regression, and the linear mixed model, as well as missing data in various designs. To design a study, researchers can apply these design effects, also known as variance inflation factors to adjust the power or sample size calculated from a two-group parallel design using standard formulas and software.

*(Eval Health Prof 26(3):239-57, 2003)*  
CSPCC Palo Alto, CA

## Analysis of Randomized Controlled Trials

PETER PEDUZZI, WILLIAM HENDERSON, PAMELA HARTIGAN, AND PHILIP LAVORI

This review paper discusses the key issues and approaches to the analysis of data from multi-site randomized clinical trials, with an emphasis on the practical considerations. The topics covered include: an overview of the principle of intent to treat, assessing the comparability of treatment groups, survival analysis, longitudinal descriptions

and analyses, permutation and exact methods, techniques for analyzing health related quality of life data, presentation and analysis of safety data, issues related to the analysis of multi-site trials, and analytic considerations for monitored trials. Many references from the literature are provided that give a more in-depth coverage of these topics.

*(Epidemiol Rev 24(1): 26-38, 2002)*  
CSPCC West Haven, CT

# PoleStriding Exercise and Vitamin E for Management of Peripheral Vascular Disease

EILEEN G COLLINS, W EDWIN LANGBEIN, CYNTHIA OREBAUGH, CHRISTINE BAMMERT, KARLA HANSON, DOMENIC REDA, LONNIE C EDWARDS, FRED N LITTOOY

**Abstract:** *Purpose:* The purpose of this investigation was to evaluate the efficacy of PoleStriding exercise (a form of walking that uses muscles of the upper and lower body in a continuous movement similar to cross-country skiing) and vitamin E ( $\alpha$ -tocopherol) to improve walking ability and perceived quality of life (QOL) of patients with claudication pain secondary to peripheral arterial disease (PAD).

*Methods:* Fifty-two subjects were randomized into four groups: PoleStriding with vitamin E, PoleStriding with placebo, vitamin E without exercise, and placebo with exercise. The dose of vitamin E was 400 IU daily. Only the PoleStriding with vitamin E and PoleStriding with placebo groups received PoleStriding instruction and training. Assignment to vitamin E or placebo was double blind. Subjects trained three times weekly for 30-45 min. (rest time excluded). Individuals in vitamin E and placebo groups came

to the laboratory biweekly for ankle blood pressure measurements.

*Results:* Results of this randomized clinical trial provide strong evidence that PoleStriding significantly improved exercise tolerance on the constant work-rate and incremental treadmill tests. Ratings of perceived claudication pain were significantly less after the PoleStriding training program. In contrast, vitamin E did not have a statistically significant effect on the subjects' ratings of perceived leg pain or treadmill walking duration. Perceived distance and walking speed and perceived physical function improved in the PoleStriding trained group only.

*Conclusion:* PoleStriding effectively improved the exercise tolerance and perceived QOL of patients with PAD. Little additional benefit to exercise capacity was realized from vitamin E supplementation.

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CSPCC Hines, IL

# Development and Validation of a Multifactorial Risk Index for Predicting Postoperative Pneumonia after Major Noncardiac Surgery

AHSAN M AROZULLAH, MD, MPH; SHUKRI F KHURI, MD; WILLIAM G HENDERSON, PHD; AND JENNIFER DALEY, MD, FOR THE PARTICIPANTS IN THE NATIONAL VETERANS AFFAIRS SURGICAL QUALITY IMPROVEMENT PROGRAM

**Abstract:** *Background:* Pneumonia is a common postoperative complication associated with substantial morbidity and mortality.

*Objective:* To develop and validate a preoperative risk index for predicting postoperative pneumonia.

*Design:* Prospective cohort study with outcome assessment based on chart review.

*Setting:* 100 Veterans Affairs medical centers performing major surgery.

*Patients:* The risk index was developed by using data on 160 805 patients undergoing major noncardiac surgery between 1 September 1997 and 31 August 1999 and was validated by using data on 155 266 patients undergoing surgery between 1 September 1995 and 31 August 1997. Patients with preoperative pneumonia, ventilator dependence, and pneumonia that developed after postoperative respiratory failure were excluded.

*Measurements:* Postoperative pneumonia was defined by using the Centers for Disease Control and Prevention definition of nosocomial pneumonia.

*Results:* A total of 2466 patients (1.5%) developed pneu-

monia, and the 30-day postoperative mortality rate was 21%. A postoperative pneumonia risk index was developed that included type of surgery (abdominal aortic aneurysm repair, thoracic, upper abdominal, neck vascular, and neurosurgery), age, functional status, weight loss, chronic obstructive pulmonary disease, general anesthesia, impaired sensorium, cerebral vascular accident, blood urea nitrogen level, transfusion, emergency surgery, long-term steroid use, smoking, and alcohol use. Patients were divided into five risk classes by using risk index scores. Pneumonia rates were 0.2% among those with 0 to 15 risk points, 1.2% for those with 16 to 25 risk points, 4.0% for those with 26 to 40 risk points, 9.4% for those with 41 to 55 risk points, and 15.3% for those with more than 55 risk points. The C-statistic was 0.805 for the development cohort and 0.817 for the validation cohort.

*Conclusions:* The postoperative pneumonia risk index identifies patients at risk for postoperative pneumonia and may be useful in guiding perioperative respiratory care.

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CSPCC Hines, IL

# A Department of Veterans Affairs Cooperative Studies Program Clinical Trial Comparing Combined Warfarin and Aspirin to Aspirin Alone in Survivors of Acute Myocardial Infarction

LOUIS FIORE, MD, MPH, MICHAEL EZEKOWITZ, MD, MARY BROPHY, MD, MPH, DAVID LU, MD, JOSEPH SACCO, MD, PETER PEDUZZI, PHD.

**Abstract:** *Background:* Both aspirin and warfarin when used alone are effective in the secondary prevention of vascular events and death following acute myocardial infarction. We tested the hypothesis that aspirin and warfarin therapy, when combined, would be more effective than aspirin monotherapy.

*Methods and Results:* We conducted a randomized, open label study to compare the efficacy of warfarin (target International Normalized Ratio (INR) 1.5-2.5 IU.) combined with aspirin 81 mg daily to aspirin monotherapy (162 mg daily) in reducing total mortality in 5,059 patients enrolled within 14 days of infarction and followed for a median of 2.7 years. Secondary endpoints included recurrent myocardial infarction, stroke and major hemorrhage. 438 of 2537 patients (17.3 percent) assigned to the aspirin group and 444 of 2522 patients (17.6 percent) assigned to the

combination group died (logrank  $p = 0.76$ ). Recurrent myocardial infarction occurred in 333 patients (13.1 percent) taking aspirin and 336 patients (13.3 percent) taking combination therapy (logrank  $p = 0.78$ ). Stroke occurred in 89 patients (3.5 percent) taking aspirin and 79 patients (3.1 percent) taking combination therapy (logrank  $p = 0.52$ ). Major bleeding occurred more frequently in the combination therapy group than in the aspirin group (1.28 versus 0.72 events per 100 person years of follow-up,  $p < 0.001$ ). There were 14 individuals with intracranial bleeds in both the aspirin and combination therapy groups.

*Conclusions:* In post-myocardial infarction patients warfarin therapy at a mean INR of 1.8 combined with low dose aspirin did not provide clinical benefit beyond that achievable with aspirin monotherapy.

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ERIC Boston, MA

# Maintenance of Patient Privacy in De-Identified Databases That Contain Study Dates

YAJIE WANG, MS, BOR-MING OU, MS, BRIAN DOHERTY, PHD,  
BOB EDSON, MA, AND PHILIP LAVORI, PHD

**Abstract:** The U.S. Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) often receives requests from outside researchers for access to final study data. In granting such a request, we must balance the desire to provide a useful database with the need to protect patient privacy and conform to the requirements of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule published by the U.S. Department of Health and Human Services.

This presentation will explain the process used to create de-identified databases from two clinical trials coordinated by the VA Palo

Alto CSP Coordinating Center, including a description of the issues faced and how we handled identifying information such as the patient's name and initials, age, Social Security Number, and dates (e.g., birth date, enrollment date, date a procedure was performed or an event occurred). The product of this exercise are SAS programs that may be used to randomly assign new identifying codes to study sites and patients within sites, and to shift all dates for a given patient by a random amount (which may be positive or negative) while keeping intact the patient's relative order of enrollment.

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CSPCC Palo Alto, CA

# A SAS Macro for Producing Data Summary Tables

YAJIE WANG, MS, LAN ZHAO, MS, SURAI THANEEMIT-CHEN, MS,  
VAISHALI KRISHNAN, BS, GALINA SHAMAYEVA, MS, AND BOB EDSON, MA

**Abstract:** The Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) conducts large scale, definitive research in multi-site clinical trials on health issues important to the nation's veterans.

To provide oversight committees and study investigators with the information they need to monitor study progress, on a regular basis CSP staff produce summaries of patient intake, patient characteristics and outcomes, and data quality. Since only the oversight committees may see results broken down by treatment group, we produce two sets of data summaries. Typically, the formats of the tables and graphs in the two sets are similar as both include summary statistics for categorical and continuous variables, and differ only in how the data are broken down (by

site in one set and by treatment group in the other).

This paper presents a SAS macro module to generate data summary reporting tables. The module resulted from discussions within the Statistical Programming Group at the Palo Alto CSP Coordinating Center with the goal of creating standardized or prototype programs to produce tabular data summaries. Given a data set (e.g., means, standard deviations, ranges, number of missing values, statistics and p-values from t tests to compare treatment groups on a set of continuous variables), a row label file, and a column heading file, this module will produce a table with options for data columns per page, column width, blank spaces between columns, and the titles, footers and page breaks.

*(Proceedings of the 2002 Annual Conference of the Pharmaceutical Industry SAS Users Group, Salt Lake City, Utah, pp 137-41)  
CSPCC Palo Alto, CA*

# Regulatory Issues for Clinical Trials in Humans

JOSEPH F COLLINS AND MIKE R SATHER

**Abstract:** Clinical trials in humans are research studies designed to evaluate two or more treatments in human participants. Major concerns in any clinical trial are the protection of study participants' safety and rights and ensuring the accuracy and validity of the data being collected. To ensure that these concerns are adequately addressed in a study, the funding institutions, the institutions where the research actually takes place, and federal and state regulatory agencies have developed regulations and guidelines for conducting human research.

In the United States, each of the granting federal departments and agencies has its own regulations and guidelines for conducting human research that must be followed. If a new drug/device is being tested or an approved drug/device is being tested for a new indication, then the study must be conducted under the rules and regulations of the US Food and Drug Administration (FDA). In cases where there is both a federal funding institution

and a new drug/device being tested, the regulations of both the funding department or agency and the FDA must be followed. These regulations for the FDA and the various federal departments and agencies can be found in the Code of Federal Regulations (CFR). A listing of the appropriate CFR for the various federal departments and agencies can be found in the instructions for federalwide assurance from the Office for Human Research Protections, Department of Health and Human Services.

Although many clinical trials in the United States are funded by federal departments and agencies, many are funded by the pharmaceutical industry. These industry studies will almost always comply with FDA regulations and the International Conference on Harmonisation guidelines that have been adopted by the FDA. In this article, some of the more pertinent regulatory issues that an investigator must address when conducting a clinical trial are described.

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*CSP CRPCC Albuquerque, NM and CSPCC Perry Point, MD*