01
THE ROLE OF THE DATA COORDINATING CENTER FOR THE SPARC REGISTRY STUDY
James R. Johnson, Barbara H. Johnson and Brenda Jamerson
Campbell University School of Pharmacy
Morrisville, North Carolina, USA

The SPARC (Study of Perfusion and Anatomy’s Role in CAD) study is a multicenter observational, registry study, begun in 2006 to recruit 3700 patients referred for a cardiovascular diagnostic imaging study. The study has two primary objectives (1) Assess the impact of Myocardial Perfusion (stress SPECT and stress PET), CT Coronary Angiography (CTA), and combined Myocardial Perfusion-CTA imaging (PET-CT) on post-test resource utilization as measured by referral to catheterization within 90-days, and (2) Determine the incremental prognostic value of stress SPECT, stress PET, CTA, and PET-CT for predicting cardiac death and nonfatal myocardial infarction at 90-days, 1 and 2 years post index test.

The Campbell University School of Pharmacy, Clinical Research Center is serving as the study data coordinating center (DCC). The DCC is involved in all phases of the planning, design, and patient follow-up for SPARC. The SPARC DCC is unique in that patient follow-up through the DCC call-center is a major function, integrated with study data management and biostatistics functions. This presentation will describe the multidisciplinary organization of the SPARC Study and operational aspects of the DCC for efficient data management processes and outcome evaluation in a complex cardiovascular imaging study.

02
IMPLEMENTING DATA STANDARDS: CHALLENGES FROM THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS), NATIONAL INSTITUTES OF HEALTH (NIH), COMMON DATA ELEMENTS (CDE) PROJECT
Selma C. Kunitz
KAI Research, Inc., Rockville, Maryland, USA

To streamline clinical trials data collection in neurological studies, NINDS, NIH together with KAI Research, Inc. initiated a CDE project. To implement the NINDS vision, KAI developed an interactive Web portal containing the core common data elements in the form of data dictionaries, data collection forms, and Manual of Procedures (MOP).

Goals of the project are to:
• Create easily accessible data collection tools for clinical investigators, with a focus on critical data elements.
• Achieve data independence through technology (XML) with data collection tools.
• Facilitate aggregation of data through data repository of completed studies

Implementation included:
• Review of NINDS studies data collection forms and definitions to identify a set of “core” data elements relevant across neurological studies.
• Literature review to identify data results as an empirical test of the data elements contained in the CDE “core” data set.
• Literature review to identify data results as an empirical test of the data elements contained in the CDE “core” data set.

Products developed:
• Data structure, XML tags, definitions that facilitate data independence and compatibility with other data standards projects (e.g. NIH Roadmap Initiative and CDISC).
• Interactive Web site to access CDE data elements, data dictionary, study forms, and MOP at www.nindscommondataelements.org. The web site will also be expanded to include data sharing procedures.
• Disease ‘spokes’ of CDEs for specific neurological disease areas.
• Training materials for investigators to ensure studies collect the fundamental data for a study.

We will address lessons learned in the implementation of the CDE, including gap analysis for NINDS studies and some of the difficulties merging existing standards in new disease areas.

03
INFORMATION TECHNOLOGY AND DATA MANAGEMENT PRACTICES OF RESEARCH NETWORKS: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT
Richard Reithinger and Steve Durako
Westat, Rockville, Maryland, USA

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with members of a sub sample of CRNs to gather detailed information about the practices that each CRN employs to organize and conduct research.
Key findings from two of the survey modules will be presented. The Information Technology instrument addressed characteristics of the network’s IT infrastructure, including hardware and software applications; numbers of users and workstations; extent of common support framework integration, system security, web site content and users; and user support services and satisfaction. The Data Management instrument asked questions regarding overall network data management operations and organization; the locus and functioning of different data management activities; data checking and validation procedures; data sharing policies and practices, including use of and barriers to use of common data elements; and other standardized practices.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and stimulates the discussion of best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources (NCRR), a component of NIH. It stems from the NIH’s commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.

04
IMAGE-BASED MULTI-CENTER CLINICAL TRIALS: IMAGE COLLECTION, DE-IDENTIFICATION, AND ARCHIVING
Kenneth W. Clark, David Gierada, Stephen Moore, David Maffitt and Fred Prior
Washington University School of Medicine, Saint Louis, Missouri, USA

Managing image-based study information presents unique challenges beyond those usually encountered in multicenter clinical-trial data collection and centralized clinical-database management. Should a site maintain its own trial-specific image archive or should it store image exams on its medical-center’s clinical archive? How does the study ensure shared images and headers are free of protected health information? Should images destined for centralized storage and analysis be delivered via secure Internet transmission or shipped on magnetic or optical media? Should images be delivered as they become available, periodically delivered on schedule, or delivered in a periodic batches? How does central-archive management coordinate with individual centers to ensure that the correct image exams and the correct number of images in each exam have arrived? How are image sets arriving at the central archive managed (workflow, quality-assurance)? Should the centralized image archive be managed by the keepers of the clinical database, or is it preferable for respective specialists to manage them separately? If separate, how are the clinical and image databases coordinated? There are more questions and no simple answers; but these questions serve merely as starting points in the planning of image-based trials. By way of example, we report our experience collecting, de-identifying, and archiving of some 48,000 chest computed-tomography (CT) exams averaging ~300 images/exam (total archive size is approximately 7 terabytes) for the U.S. National Cancer Institute’s Lung Screening Study of the National Lung Screening Trial involving 10 screening centers. We believe the sharing of this experience may be valuable to others involved in the planning and management of image-based clinical trials.

05
AN INTEGRATED DATA MANAGEMENT SYSTEM FOR A CLINICAL TRIAL IN A GENERAL PRACTICE SETTING
Elizabeth C. Griffith, Philip Ryan, Brian McDermott, Caroline Laurence and Briony Glastonbury
The University of Adelaide, Adelaide, Australia

The Data Management & Analysis Centre provides integrated data management services to clients conducting large-scale health related research. Staff at the Centre include statisticians, epidemiologists, data managers, systems analysts, programmers and data entry staff. In 2005, the Commonwealth Department of Health and Ageing funded the POCT clinical trial to assess the safety and clinical and cost effectiveness of Point of Care Testing for hyperlipidemia, diabetes and INR management, using seven tests, in a general practice setting. The trial is conducted in 60 general practices across three Australian states in urban, rural and remote settings. The trial is collecting data on almost 5000 patients with the potential for almost 40000 pathology and POCT tests being performed during the study.

We discuss the design and implementation of the data management system designed for the trial. We describe and demonstrate the use of a generic facility that allows the flexibility to incorporate new trial events into the data management system at any point in the life of the trial.
Using imputation to estimate binary response from longitudinal data with non-ignorable missing values, with application to a migraine trial
Xiaoyin Fan1 and Fang Fang2
1Merck Research Laboratories, North Wales, Pennsylvania, USA
2University of Wisconsin-Madison, Madison, Wisconsin, USA

In migraine trials both headache responses at individual time points and the sustained response are important measures. Usually patients are asked to record headache scores at individual time points plus headache recurrence, if any, during the follow up period. In the case of missing recurrence values, a common and intuitive approach treats the missing value as failure if any of the recorded pain responses are failures at any timepoint during follow-up. However, this approach will cause inconsistent estimation in the sustained pain response even if the headache scores and recurrence are missing completed at random (MCAR).

The estimation methods using complete cases only or generalized estimation equation (GEE) are inconsistent and inefficient since the missing mechanism is usually non-ignorable.

Taking advantage of the special structure of the binary data, we proposed several consistent methods for estimating the sustained pain response. The proposed approaches use either direct formulas or single imputation to calculate consistent estimators and they do not require model assumptions for the missing mechanism or specification of the correlation structure between the repeated observations. Simulation studies were conducted under different response profile and missing patterns over time. The proposed single imputation method is demonstrated to be robust and effective in reducing both bias and mean squared error (MSE) from existing methods.

Impact of measurement errors in phase I dose finding trials: algorithm vs model based approach
Xavier Paoletti
Institut National du Cancer, Boulogne, France

Background The main endpoint of phase I clinical trials is toxicity, most often graded on a 5-level scale (Common Toxicity Scale). Highest grades are denoted Dose Limiting Toxicity (DLT). Grading is performed by the investigator and implies quantitative (number of white blood cells), or qualitative (fatigue, depression) aspects. In addition, imputability to the investigated treatment is often required to determine if the toxicity really limits dose escalation. Measurement errors have then been described that depend on the type of toxic event. In this communication we compare the impact of such measurement errors on the Maximum Tolerated Dose (MTD) recommended for further studies when respectively a 3 algorithmic method and model-based designs such as the Continual Reassessment Method (CRM) are used. We also propose a way to take into account the degree of uncertainty associated with a toxic event when a model-based approach is used.

Methods We performed a simulation study to assess the impact of such measurement errors on the final dose recommendation and on trial duration. We investigated several potential dose-toxicity relations under various measurement error hypotheses.

Results We show that algorithmic design appears to be more robust to rare measurement errors. When the risk of error increases, these designs entail recommendation errors larger than those observed with the CRM. Impact of the stopping rule on the 3 design is highlighted.

Conclusions Measurement error may have a considerable impact on the identification of the dose to be recommended for phase II trials and thus jeopardize future clinical development. Both approaches are very sensitive to such errors. Adequate methods are needed.

Use of non-compliance adjustment to estimate subgroup effects
Timothy R. Church and Steven J. Mongin
University of Minnesota School of Public Health, Minneapolis, Minnesota, USA

Using randomization assignment as an instrumental variable provides a powerful method for adjusting effect estimates for non-compliance in randomized clinical trials. Underlying this method is an assumption that non-compliance is purely a selection effect and, hence, has no effect on the non-compliers. Some interventions have a direct physiologic effect only on a subset of the subjects who comply. For example, cancer screening tests only affect those that have a positive test. By considering the analogy between complying with the assigned intervention and exhibiting a positive test, an unbiased estimate of the intervention effect on cancer mortality among those with a positive screening test can be derived. We derive such an estimate and apply it to test positivity in a study of colon cancer screening. We discuss the assumptions necessary for the unbiasedness of the estimator and evaluate the sensitivity of the method to violations of the assumptions. We also point out other situations in which this method could be used.
USE OF CAUSAL MODELLING IN TRIALS OF COMPLEX INTERVENTIONS
Graeme S. MacLennan and Craig Ramsay
University of Aberdeen, Aberdeen, UK

Background In randomised trials of complex interventions (such as non-drug technologies), it is likely that some participants will not receive the intervention to which they were randomised. Some reasons for this are preferences for alternative treatment, waiting list delays or the need to convert from one surgical procedure to another (eg from a laparoscopic procedure to an open procedure). Whilst an intention to treat analysis (ITT) is the most appropriate and unbiased test of the benefit of the policy change, investigators are often also interested in the efficacy (benefit of actually receiving) the intervention. Over the last decade complier average causal effect (CACE) models have been proposed as a potentially useful way of determining efficacy. There is currently little evidence on the impact of applying such models to randomized trials of complex interventions.

Methods A number of approaches to modelling the data were investigated (ITT, per protocol, as treated (AT), CACE models, G-estimation) using a number of trial datasets. Factors associated with non-adherence were also investigated.

Results For an exemplar double-blind trial, the CACE estimates were in between the intention to treat and per protocol estimates (odds ratio (95% confidence interval) ITT 0.95 (0.79 to 1.14); CACE 0.85 (0.52 to 1.38); AT 0.74 (0.58 to 0.96)). For the unblinded surgical trials, CACE estimates were usually greater than other estimates. Baseline quality of life scores were strong predictors of adherence in the trials.

Conclusion CACE models can be used for estimating efficacy of interventions in trials of complex interventions, but investigators should be aware of the required assumptions and interpretations.

HANDLING MISSING BINARY OUTCOMES IN INFECTIOUS DISEASE STUDIES OF PROPHYLAXIS IN HIGH RISK POPULATIONS
Patricia L. Stephenson
Rho, Inc., Chapel Hill, North Carolina, USA

In clinical trials, the outcome of interest may often be missing for some patients who do not complete the study. Such withdrawals may be due to events such as death, adverse events, lack of efficacy, and early improvement. Often, studies may include a plan for obtaining information needed for the outcome for subjects who withdraw early. High risk populations, such as ICU patients, may present a further challenge since subjects may more often experience serious co-morbid conditions, which prevent assessment of the outcome or even may be at a greater risk for death during the study. The choice of an appropriate approach to analysis that adjusts for such missing outcomes does not solely depend on an evaluation of the biases of available methods but rather should be based on the overall goal of the study; the clearly identified a priori hypothesis of interest; the reasons, timing, and nature of the withdrawals; and consideration of the disease setting of application. In this paper, we review methods for adjusting for missing binary outcomes in the context of randomized prophylaxis studies of infectious diseases in high-risk patients. The Bacteriology and Mycology Study Group (BAMSG) 4–02 study is used to illustrate the methods and guidelines are provided for their appropriate use.

METHODS OF BLINDING IN REPORTS OF RANDOMIZED CONTROLLED TRIALS ASSESSING NONPHARMACOLOGICAL TREATMENTS: AN ANNOTATED BIBLIOGRAPHY
Isabelle Boutron1, Lydia Guittet1, Candice Estellat1, David Moher2, Asbjørn Hróbjartsson3 and Philippe Ravaud1
1INSERM, Paris, France,
2University of Ottawa, Ottawa, Canada
3Nordic Cochrane Centre, Copenhagen, Denmark

Background Blinding is a cornerstone of therapeutic evaluation as lack of blinding can bias treatment effect estimates. An inventory of the blinding methods is necessary to help trialist to conduct high quality clinical trials and readers to appraise the quality of published trials.

Objective To systematically appraise the strategies used to obtain blinding in randomized controlled trials of non-pharmacological treatment.

Design Systematic review
Data sources Medline and the Cochrane Methodology Register.

Review Method Reports of randomised controlled trials assessing nonpharmacological treatment with blinding published in 2004 in high-impact-factor journals were selected. A standardized abstraction form was used to extract data. The blinding methods were classified a posteriori according to whether they primarily concerned blinding of patients, healthcare providers or other caregivers and blinding of assessors of the main outcomes.
Results A total of 145 articles were identified. The method of blinding was described in 123 reports. Methods of blinding of patients and/or healthcare providers and/or other caregivers concerned mainly use sham procedures and blinding patients to the study hypothesis. For surgical interventions, the sham procedures consisted mainly in a simulation of the intervention with a standardization of postoperative care. For participative interventions such as rehabilitation or psychotherapy, the sham procedures were either a similar attention-control intervention or a placebo with a different mode of administration. Trials assessing devices reported various placebo interventions such as use of sham prostheses, identical apparatus (identical inactivated machine or use of activated machine but with a barrier to block the treatment) or simulation of using a device. Use of a placebo control intervention not identical to the active treatment with patients blinded to the study hypothesis could also be a solution in assessing nonpharmacological treatment. The methods reported for blinding outcome assessors mainly relied on centralized assessment of paraclinical examinations, clinical examination (i.e., use of video, audiotope, photography) or adjudication of clinical events.

Conclusions This review classifies blinding methods and provides a detailed description of methods that could overcome some barriers of blinding in clinical trials assessing nonpharmacological treatment.

12

HOW TO REALIZE HOMOGENEOUS TREATMENT WITHIN RANDOMIZED GROUPS
IN SURGICAL TRIALS – WHAT CAN BE DONE?
Markus K. Diener, Hanns-Peter Knaebel and Christoph M. Seiler
Study Centre of the German Surgical Society (SDGC)
University of Heidelberg, Heidelberg, Germany

Background In clinical trials, biases fall into four major categories: selection bias, performance bias, detection bias, and attrition bias. Performance bias occurs if the interventions under study as well as additional co-interventions, such as peri-operative treatment, are non-standardized or provided differentially to one group. Thus, variation in the conduct of surgical interventions may cause variability and bias in estimates of effect within single or between multiple surgical trials addressing the same clinical question. The objective of this study is to identify and describe methods for standardization in complex surgical trials.

Methods Two randomized controlled trials (RCT) conducted by the Study Centre of the German Surgical Society (SDGC) explicitly applied methods against performance bias. The INSECT-Trial was designed to evaluate surgical techniques for abdominal closure and the issue how the standardized suture technique could be monitored had to be resolved. The DISPACT-Trial was set out to compare two surgical techniques of distal pancreatectomy. Thus, dealing with a complex surgical intervention, standardization of intra- and peri-operative surgical care was elementary for the trial design.

Results The INSECT-Trial represents an example of a large and pragmatic surgical trial. Systematic briefing of all participating surgeons with hands-on sessions and teaching with video tapes and treatment manuals during pre-study workshops accounted for harmonization at the start of patient treatment. A standardized suture material was used to assess an abdominal incision/suture length ratio of 1:4 to monitor technique adherence during conduction. In addition to well-defined treatment manuals and a representative set of clinical endpoints, the DISPACT-Trial is characterized by intra-operative digital photo-documentation of the pre-specified surgical technique.

Discussion Surgical trials require a unique methodology for the realization of treatment equality and standardized interventions in comparison to pharmacological trials. Besides rigorous definition of all study relevant procedures and endpoints, teaching of participating surgeons before and during the trial might also reduce performance bias. Since attending surgical monitors are expensive and not feasible in most cases, intra-operative photo-documentation might be a reasonable alternative.


13

THE ROLE OF PLACEBO IN SURGICAL TRIALS: INSIGHTS FROM THE KORAL STUDY
Marion Campbell, Zoë Skea, Brian Cuthbertson, Vikki Entwistle, Alasdair Sutherland and the KORAL Study Group
University of Aberdeen, Aberdeen, Scotland

The role of placebo in drug trials is widely recognised, and the placebo-controlled trial is considered the gold standard design in many circumstances. The place of placebos in surgical trials, however, remains controversial with widespread debate about whether, and in what circumstances, such designs are ethical. In 2004, the UK NHS Health Technology Assessment Programme announced its wish to commission a multicentre placebo-controlled trial of arthroscopic lavage for the management of knee osteo-arthritis. Arthroscopic lavage is a surgical procedure which involves washing out the knee space to remove any loose debris. A previous single-surgeon placebo-controlled trial conducted in the USA had shown no evidence of benefit of the technique over placebo. Recognising that conducting such a trial in the UK might be problematic, our research group was funded to undertake a feasibility study involving focus groups, interviews and surveys to ascertain the acceptability of a placebo-controlled

http://ctj.sagepub.com

Clinical Trials 2007; 4: 371–455
design to key stakeholder groups (including surgeons, anaesthetists, prospective participants and members of research ethics committees). A number of key issues emerged from the feasibility work including: 1) the form the placebo should take to strike an appropriate balance between maximising the mimic and minimising the risk – this was especially pertinent for the choice of anaesthesia; 2) the information participants would require to give adequately informed consent; 3) the requirement for members of different multidisciplinary teams to jointly agree to recruit patients (and the implications for the trial this may have); and 4) the importance of the views of ethics committees. These factors will be discussed, together with the generalisable lessons to surgical placebos more broadly.

SHAM VERSUS NO-TREATMENT CONTROLS IN OPHTALMOLOGY CLINICAL TRIALS
Barbara S. Hawkins, Sandra Reynolds and Neil Bressler
The Johns Hopkins University, Baltimore, Maryland, USA

In randomized trials of pharmacologic agents, inactive placebos are an accepted comparator to minimize the “placebo effect”. When the test intervention is one in which the delivery method itself involves risk, the choice of an appropriate control is challenging.

Hrobjartsson and Gøtzsche reviewed 114 trials that included random assignment of control patients to placebo or no treatment and masked assessment of outcomes. They concluded that, in most situations (subjective or objective binary outcomes and objective continuous outcomes), there was no significant “placebo effect”. Clinical trials for retinal diseases have proceeded from evaluation of one-time treatments (e.g., laser photoagulation or surgery) to intraocular implanted devices and monthly intraocular injections. No clinical trials in these conditions (or other ophthalmologic conditions) have assigned patients in the control arm randomly between sham (placebo) and no treatment to estimate the “placebo effect”.

To provide estimates of the “placebo effect” in a retinal condition that affects central vision in older adults, we are analyzing control-arm databases from 5 clinical trials, 2 industry-sponsored (sham controls) and 3 NIH-sponsored (no-treatment controls). Both objective and quasi-objective outcomes and binary and continuous outcomes were assessed in these trials. Sham controls (228 “Cases”) have been matched on all known predictors of outcomes to one or more no-treatment “Controls”. One of the trials (227 Controls) was conducted concurrently with the sham-controlled trials; two were conducted a decade earlier (288 Controls). Case-Control comparisons are used to estimate the “placebo effect” for multiple outcomes. Ideally, designers of future clinical trials in ophthalmology will randomize patients in the control arm to sham versus no-treatment, when no effective treatment is available, to provide better estimates of “placebo effects”.

ISSUES CONCERNING PILOT STUDIES IN PUBLICLY FUNDED NON-DRUG RANDOMISED CONTROLLED TRIALS
John D. Norrie, Alison McDonald and Gladys McPherson
University of Aberdeen, Aberdeen, UK

Randomised controlled trials of non-drug interventions can be difficult to design and conduct. Recently published research (Campbell, HTA Monograph, in press) reported two out of every three major UK publicly funded trials failed to recruit to target. Funders look for firm evidence for reassurance of feasibility, with all aspects appropriately thought through and processes tested. It is becoming obligatory for a formal pilot or feasibility study to be included or proposed in a funding submission. However, although the science of design of ‘full’ trials is well developed, this does not seem true for pilot or feasibility studies. In many settings the design of an informative pilot or feasibility study can be at least if not more challenging than designing a full trial. Often disproportionately little effort is put into the pilot design, and the pilot data then interpreted in an uncritical fashion. This presentation describes different pilot/feasibility designs (from discrete, short term ‘throwaway’ pilots to test very specific elements through to so-called internal pilots designed to be incorporated into the full trial). We emphasise the importance of a pilot protocol, including clear statements regarding what the pilot is not intended to address. Consideration is given to what size pilots need to be to address their goals, both participants (and how they may be selected) and for multicentre trials, how many pilot centres. Distinction is drawn between data to check assumptions behind the full trial (such as measures of variability, and event rates), and data on processes (such as whether trial outcomes are measurable in the allotted time, clarity of case report forms). Emphasis is placed on ensuring that trialists do not needlessly duplicate what is available with precision elsewhere – e.g. getting potential throughput and eligibility data from national and local routine resources to inform recruitment projections.

REPORTING OF SUBGROUP ANALYSES IN THE NEW ENGLAND JOURNAL OF MEDICINE
Rui Wang and Stephen Lagakos
Harvard University, Boston, Massachusetts, USA

Background Subgroup analyses can provide useful information about the heterogeneity of treatment group differences among the levels of baseline characteristics. However, misinterpretation can often occur due to data
driven hypotheses, inappropriate statistical methods, or failure to account for multiple testing. This leads to suspicion of subgroup analysis findings, especially when the methods and results are not clearly reported.

**Methods** We reviewed original articles published in the NEJM between July 1, 2005 and June 30, 2006 that reported primary results from randomized clinical trials. We recorded characteristics of the trial, whether a “significant” result was reported for a primary endpoint, and whether any subgroup analyses were reported. For trials reporting subgroup analyses, we ascertained the number of subgroup analyses, the statistical methods used, and where and how the results were presented and interpreted.

**Results** Ninety-seven trials were reported in 95 papers. Larger (p = 0.02) and multi-center trials (p = 0.05) were significantly more likely to report subgroup analyses. The number of subgroup analyses undertaken was unclear in 9 (15%) papers. In 40 (68%) trials, it was unclear whether any of the subgroup analyses were pre-specified; in 3 (5%) others it was unclear whether some subgroup analyses were pre-specified. Interaction tests were consistently used to assess treatment difference heterogeneity in 16 (27%) trials, and used for some subgroup analyses in 11 (19%) trials. Fifteen (25%) trials claimed heterogeneity for at least one patient subgroup, with only four based on interaction tests.

**Conclusions** Considerable improvement in conducting and reporting subgroup analyses is needed and can be accomplished by establishing and enforcing editorial guidelines. Proper subgroup analyses would provide caregivers and researchers with valuable and interpretable information, and thereby improve patient care.

---

**S 17**

**A NONPARAMETRIC FRAMEWORK FOR QUANTILE EQUIVALENCE TRIALS WITH APPLICATION TO BRIDGING STUDIES FROM HIV-INFECTED ADULTS TO CHILDREN**

Lixia Pei and Michael D. Hughes

Harvard University, Boston, Massachusetts, USA

Many bridging clinical trials are designed to evaluate whether a proposed dose for use in one population, e.g., children, gives similar pharmacokinetic (PK) levels, or has similar effects on a surrogate marker as an established effective dose used in another population, e.g., adults. For HIV bridging trials, because of the increased risk of viral resistance to drugs at low PK levels, the goal is often to determine whether the doses used in different populations result in similar percentages of patients with low PK levels. For example, it may be desired to confirm that a proposed pediatric dose gives approximately 10% of children with PK levels below the 10th percentile of PK levels for the established adult dose. However, the 10th percentile for the adult dose if often imprecisely estimated in studies of relatively small size, but this imprecision is often ignored in analysis. Little attention has been given to the statistical framework for such bridging studies. In this paper, we provide a formal framework for such as these bridging trials which aim to establish equivalence. We show that the error rate in accepting a dose when it is truly unacceptable is inflated, often considerably, by ignoring the imprecision in estimated adult quantile. A two-sample nonparametric test for the small quantile equivalence trial is proposed using a perturbation resampling method based on asymptotically pivotal quantities. Simulation studies show that our method provides decision error rates very close to the desired value and is a considerable improvement over the error rates obtained when the imprecision in estimating $\alpha$ is ignored.

---

**S 18**

**SOURCES OF BIAS IN CLINICAL TRIALS: INAPPROPRIATE USE OF INTERIM DATA AND/OR DATA MONITORING COMMITTEE RECOMMENDATIONS IN RANDOMIZED CONTROLLED TRIALS**

Puvan Tharmanathan, Melanie Calvert, John Hampton, and Nick Freemantle

University of Birmingham, Birmingham, UK

Interim analysis of accruing randomized controlled trial (RCT) data, often performed by independent Data Monitoring Committees (DMC), is important to ensure patient safety. It has been suggested that the role of the DMC should also include advising on and recommending protocol changes. Major regulatory agencies have recently cautioned against such changes in the context of drug development as protocol amendments based on interim review can introduce bias and complicate interpretation of trial results. We conducted a systematic within-journal search of 7 major publications: BMJ, Circulation, CID, JAMA, JCO, Lancet, and NEJM (including all RCTs between June 2000 and June 2005), to examine the extent and nature of inappropriate use of interim data that may have led to protocol amendments and potentially biased trial results. 1682 RCTs were identified, of which 572 reported use of some form of interim analysis and/or a DMC. 28 trials (randomizing a total of 79396 patients) were identified as having inappropriate use of interim data (24 of these cases had formal DMCs). Our review shows that the reported use of interim analysis/DMCs has been increasing in recent years and inappropriate use of interim analysis does occur in practice. In most of these, some form of sample size re-estimation (SSR) was recommended, including examples where treatment arm specific interim data was used as a basis for the SSR. Four trials also report changes to trial endpoints. Besides this, more generally, the reporting of interim analyses requires formalizing through editorial action.

---

http://ctj.sagepub.com

Clinical Trials 2007; 4: 371–455
THE CHALLENGES OF FOLLOW-UP IN A MULTICENTRE RANDOMISED CONTROLLED TRIAL
Christine Tassopoulos
University of Toronto, Toronto, Ontario, Canada

Follow-up of study patients is an integral part of many randomised controlled trials. The Twin Birth Study (TBS) is an international multicentre randomised controlled trial which seeks to determine in women expecting twins, whether a policy of planned caesarean section decreases the likelihood of perinatal or neonatal mortality or serious neonatal morbidity, compared to a policy of planned vaginal birth.

Follow-up in TBS includes two components. First, the women recruited are asked to complete a structured questionnaire to determine satisfaction with the method of delivery, quality of life, depression, breast feeding, and the occurrence of problematic incontinence at both 3 months and 2 years postpartum. Second, the women are asked to complete a screening questionnaire to assess the neurodevelopmental outcomes of their twins at 2 years corrected age.

The primary goal at the Data Coordinating Centre (DCC) was to facilitate comprehension and ease of performing the follow-up at participating sites. Tasks prior to follow-up implementation included forms translation, corrected age calculation, programming of follow-up reminders and creation of a scoring program. Promotional items and newsletter reminders were sent as aids to help minimize loss to follow-up.

The presentation will outline the challenges we at the DCC overcame to make the follow-up a success. These include promoting follow-up during ongoing recruitment, implementing the follow-up at sites during different time intervals, ensuring the completion of the questionnaires within the appropriate date window and facilitating the ease of the follow-up for 75 sites in 20 countries requiring questionnaires in 13 languages.

STATISTICAL AND SAFETY CONSIDERATIONS FOR STOPPING AN ASTHMA STUDY: THE ACRN SLiMSIT TRIAL
Susan Kunselman, Vernon Chinchilli, Ronald Zimmerman, Elliot Israel and Aaron Deykin for The Asthma Clinical Research Network (ACRN)
Pennsylvania State College of Medicine, Hershey, Pennsylvania, USA

The Salmeterol and Leukotriene Modifiers vs. Salmeterol and Inhaled Corticosteroids Treatment (SLiMSIT) trial of the ACRN was a randomized, double-blind, $2 \times 2$ cross-over study of subjects with moderate persistent asthma initiated in September 2002. The primary outcome was time to treatment failure where each subject was evaluated for treatment failure (a composite measure of asthma control) on each of the two treatment regimens. A Data and Safety Monitoring Board (DSMB) was formed to monitor the study. No planned interim analyses were included in the original protocol. In January 2003, GlaxoSmithKline (GSK) and the FDA MedWatch program issued a safety alert concerning salmeterol, one of the SLiMSIT study drugs. An interim analysis of the GSK Salmeterol Multi-center Asthma Research Trial (SMART) had revealed that salmeterol might be associated with an increased risk of life-threatening asthma episodes or asthma-related deaths, particularly in some patient subgroups. The FDA subsequently ordered a black box warning on salmeterol packaging.

Following the salmeterol safety alert, the ACRN Steering Committee and the DSMB temporarily suspended recruitment for the SLiMSIT trial and took several measures to enhance subject safety monitoring, including the introduction of formal interim analyses every three months. The trial ultimately was stopped prematurely on the basis of results from the third planned analysis.

In this presentation we will discuss the impact of the SMART study results on the DSMB's monitoring process and the actions taken by the ACRN to ensure continued subject safety. We will summarize the results of the SLiMSIT interim analyses and discuss the considerations that led to terminating the trial.

SAFETY MONITORING IN A LARGE INTERNATIONAL COLLABORATIVE CLINICAL TRIALS NETWORK
Heidi Krause-Steinrauf, Brett Loechelt, Naji Younes and Scott Quinlan for Type 1 Diabetes TrialNet
The George Washington University, Rockville, Maryland, USA

Type 1 Diabetes TrialNet is a large, international collaborative research network that conducts Phase 1, 2 and 3 clinical trials in type 1 diabetes mellitus (T1DM). Two target study populations are enrolled for interventions: newly diagnosed patients with T1DM, and individuals at risk for developing T1DM. Rigorous safety monitoring is essential as: 1) children and adolescents are the predominant target population of interest, 2) interventions (e.g. immunosuppressive agents) have potentially serious risks including reactivation of viruses, 3) “healthy” individuals (other than being identified as being at increased risk for developing T1DM) are being treated in prevention trials, 4) little data are available from previous studies of experimental agents in children with T1DM, and 5) safety data are generated from multiple laboratories and clinical sites requiring central monitoring and sometimes necessitating review and interpretation by experts.
To effectively and simultaneously monitor safety for multiple trials, TrialNet has employed multiple monitoring processes. We will describe:

- the role of the medical monitor,
- the role of the infectious disease consultants,
- the role of the Safety Monitoring Committee, and
- safety reviews by the Data and Safety Monitoring Board.

We will present the initiatives and strategies undertaken by the Coordinating Center and TrialNet Study Group to train clinical sites in protocol monitoring requirements, adverse event (AE) reporting processes, and we will describe real-time monitoring via a high security web-based portal for safety data generated by central laboratories and clinical sites. We will also discuss the review and adjudication process for industry-reported severe AEs of agents under study and the choice of a grading/coding system for AEs.

22  
A MODEL FOR STREAMLINING SERIOUS ADVERSE EVENT (SAE) REPORTING  
Chad Stimmler, Ann Jenckes, Dawn Caron-Fabio, Margaret Isaacs and Roger Wilson  
Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Historically, SAE reporting at Memorial Sloan-Kettering Cancer Center (MSKCC) was a cumbersome task that included data entry by various research staff. First, research assistants entered data into the institutional data repository, the Clinical Research Database (CRDB). Second, investigators submitted the information to the Institutional Review Board (IRB) in memo format. Finally, IRB staff re-entered the data into uncoded datasheets and a copy of each report was distributed during IRB meetings.

In 2005, we began addressing the issues associated with the methods of collecting, submitting, and storing SAE data. We reformed the reporting requirements after the implementation of the institutional Protocol Information Management System (PIMS). PIMS is a system that tracks all aspects of the IRB, including critical SAE data and reports. In January 2006 we mandated the submission of all data via the CRDB SAE form and began working on an enhancement with MSKCC’s computing staff to link CRDB and PIMS. By linking the two systems, SAE data is automatically transferred from the point of entry (CRDB) to PIMS for review by IRB members and staff.

In this presentation we will provide a model for streamlining SAE reporting, discuss the various challenges we faced, and describe the advantages of the new reporting process. We will also present our future goals and ideas for the continued improvement of SAE reporting.

23  
AUTOMATED ADVERSE EVENT MANAGEMENT IN MULTI-SITE TRIALS  
Wenle Zhao, Catherine Dillon, Bonnie Waldman and Keith Pauls  
Medical University of South Carolina, Charleston, South Carolina, USA

An especially challenging component of clinical trial management is balancing data accuracy with timely reporting of adverse events (AEs). We have developed an automated AE processing module within a central web-based data management system to coordinate the activities of AE data collection, reporting, medical safety monitoring, and filing of MedWatch reports.

Under this system, AEs are reported through the study website within a specified timeframe. For serious adverse events (SAEs), an automated email is sent to an internal clinical expert who reviews the report and other clinical data as needed. If the reviewer feels the report is inadequate, the site is instructed to supplement/edit the information.

When the report is complete, independent Medical Safety Monitors (MSMs) are notified electronically and requested to vote as to whether the event is serious, unexpected and related to study drug. If a MedWatch is needed, the system generates the form which is pre-populated with clinical data from the study database, and the site is notified to review it.

AE reports fall into three categories: new AE, follow-up report, and error correction of an existing report. If a MedWatch form was previously filed for an AE, a follow-up MedWatch is automatically generated for follow up reports and error corrections. If a MedWatch form was not previously filed for a SAE, a follow-up report or error correction will return the AE to the MSMs for further review.

We have developed this system for the Albumin in Acute Stroke (ALIAS) trial which is a Phase III randomized multicenter clinical trial of human albumin for neuroprotection in acute ischemic stroke funded by the National Institute of Neurological Disorders and Stroke (U01 NS40406, U01 NS054630).

24  
CONTROLLING FOR TYPE I ERROR WITH TWO STRONGLY ASSOCIATED CO-PRIMARY ANALYSES  
David Oakes  
University of Rochester, Rochester, New York, USA

We consider a recently conducted clinical trial involving comparison of a single active treatment with placebo. The trial had a single primary outcome variable but two co-primary analyses, the first including all subjects...
enrolled, the second including only those subjects satisfying more restrictive inclusion criteria. We discuss approaches to controlling the total Type I error for these two highly dependent analyses.

25

A LOOK AT THE STATISTICAL ANALYSIS PLAN
Nicole Close
US Army Medical Research and Material Command, Fort Detrick, Maryland, USA

For the analysis of clinical trial data, appropriate statistical methods are critical for correct interpretation of final results. The protocol should include objectives, primary/secondary endpoints, sample size, power, interim analyses, and an overall statistical analysis approach. Often, an accompanying statistical analysis plan (SAP) is not written, written and/or reviewed by inappropriate members of the trial team, or is written in various formats within the same organization and/or product development line.

Although not necessary for all trials, it is good practice to have an accompanying SAP for the protocol. The SAP is the trial’s comprehensive and detailed document of the methods for and presentation of the data analyses to ensure that they are conducted in a scientifically valid manner and that all decisions for the analyses are documented. Details of the SAP include: definition of study objectives/endpoints, endpoint measurement, sample size/power, data transformations, statistical tests and software, scientific and statistical accounting for missing data, withdrawals and outliers, multiple comparisons, statistical inference for one-tailed/two-tailed tests, subgroup analyses, safety analyses, additional planned analyses (e.g. pharmacokinetic and pharmacodynamic), reporting conventions, references, and planned listings, tables and figures.

To maintain consistency within an organization, and especially for each product, it is important to develop a standard SAP template. Having one template, that is modifiable for applicability of a Phase I, II, III or IV trial, with proposed tables, listings and figures, allows for the trial team to have a clear and documented path to the final report prior to data lock and unblinding, for consistency within an organization, and for taking a product from Phase I through Phase IV development. A well written, standard, documented, and approved SAP is a recipe for success.

26

REAL-TIME PREDICTION OF PATIENTS ACCRUAL AND TRIAL LENGTH THAT MINIMIZES COST IN RANDOMIZED CLINICAL TRIALS
Gui-Shuang Ying
University of Pennsylvania, Philadelphia, Pennsylvania, USA

In clinical trials with time to event as an outcome, the statistical power/sample size calculation is often determined by the number of events, and many trials are designed to end upon the occurrence of a pre-specified number of events. Reaching the targeted number of events is dependent on the total number of patients accrued and the length of follow-up of enrolled patients. However, accrual costs may differ greatly from follow-up costs depending on the nature of the trial, which suggests that there may be an optimal combination of accrual and length of follow-up that minimizes the cost associated with the conduction of a trial. As the disparity between accrual and follow-up costs increases, this type of determination becomes increasing important to make the conduction of a trial more cost-effective.

We propose a real-time prediction approach by using the accumulated data from the trial itself, it involves: (1) simulation of time to enrollment, time to event and time to loss of follow-up for each subject assuming non-constant enrollment and exponential in survival and loss of follow-up; (2) the determination of time to reach the planned number of events; (3) the prediction of total cost of a trial, which combines the cost on accrual and follow-up of patients until targeted number of events is reached. We demonstrate the methods using Monte Carlo studies to examine the impact of accrual rate, event rate and cost ratio of accrual to follow-up on the predicted cost of a trial, which may provide useful guidance in planning and conducting a trial.

27

BUSINESS INTELLIGENCE: STATISTICAL APPROACHES FOR DECISION-MAKING IN DRUG DEVELOPMENT
David Manner, Francois Vandenhende, Ming-Dauh Wang and Fabian Tibaldi
Eli Lilly and Company, Indianapolis, Indiana, USA

During drug development, important business decisions are taken as to whether, when and how to invest resources. Examples of such decisions may include: Is our drug’s efficacy better than or comparable to that of a marketed compound so as to justify its further investment? What is the dose range that provides the minimum required safety and efficacy profile? How can data from past studies for this compound be incorporated to make an investment decision that utilizes all available information? Should we manufacture phase III clinical trial material at risk, before end of phase II study?
Business Intelligence (BI) consists of a strategy for gathering, providing access to, and analyzing data for the purpose of better decision making. BI bridges the gap between data analyses and decision-making. Within the framework of drug development, better decisions may be taken by maximizing the value of all historical and current information on the drug candidates. We present a methodology to implement BI and the Bayesian statistics concepts that enable the delivery of informative business solutions. Examples will be given as to how this can be accomplished.

**28 THE IMPACT OF SYSTEMATIC TREATMENT INTERRUPTIONS DURING A CLINICAL TRIAL**

Bruce Thompson and Renee Rees  
Clinical Trials & Surveys Corp, Baltimore, Maryland, USA

A clinical trial testing the efficacy of two treatments or a treatment versus a placebo, may have a situation where treatment administration in the two groups is suspended. When this happens, an immediate question arises about the impact of this suspension on the original study design. Here we have developed a simple model using a binary response variable and a conservative assumption that the treatment effect is immediately lost upon suspension of treatment and immediately regained when treatment is reinitiated, to derive a formula showing the impact of treatment suspension on the original study design. The result is similar to the statistical treatment of medication crossovers when designing a clinical trial. That is, the effective sample size for the study is reduced by the square of one minus the proportion of active treatment patients whose end point is measured during the suspension period.

Since the calculation can be made in the absence of interim treatment-efficacy information, it is possible to make an administrative adjustment to the sample size using methods similar to those developed by Lachin and Foulkes or to assess the change in power that has occurred from the original calculations due to the treatment suspension. This will allow the investigators to decide whether the trial can continue using the originally specified numbers of patients or whether the sample size must be changed.

We also explore the effect of treatment suspensions on time-to-event data, and look at a case where treatment suspensions create increases in risk for the primary endpoint.

**29 SIZING SIMPLE TRIALS TO DEVELOP ADAPTIVE TREATMENT STRATEGIES**

Janet Levy, Susan Murphy, Carl Pieper, Yuliya Lokhnygina and Alena Scott  
Center for Clinical Trials Network, Bethesda, Maryland, USA

Adaptive treatment strategies are sequences of treatments where patient’s responses to previous treatments determine subsequent ones. Previous authors have advocated sequential multiple randomized trials (SMART) to support the development of these strategies. The purpose of this presentation is to demonstrate the formulation and calculation of required sample sizes for very simple SMART trials. We also demonstrate the importance of assumptions about percentages of participants who might respond well to the first treatment (“intermediate response rates”) on these sample size calculations. In the first section, we consider the development of an adaptive treatment strategy consisting of a sequence of two treatments. A SMART design is presented which permits us to pose one of four potential primary research questions: (1) Which initial treatment produces the best long term outcome in the presence of prespecified subsequent treatments? (2) Considering only participants failing to respond to specified initial treatments, which subsequent treatment produces the best long term outcome? (3) Which of two prespecified sequences of treatments (“strategies”) produces the best long term outcome? (4) Which of four possible sequences (“strategies”) produces the best long term outcome? In the second section we translate each potential primary research question into a statistical hypothesis. Formulas for test statistics and sample size estimation are presented. In the third section, we present simulations demonstrating the effects of mis-specifying intermediate response rates on power, even when longer term outcomes are correctly anticipated. We conclude with recommendations for future research.

**30 CONFIDENCE INTERVALS AND POINT ESTIMATES FOLLOWING AN ADAPTIVE GROUP SEQUENTIAL TEST**

Cyrus Mehta  
Cytel Software Corporation, Cambridge, Massachusetts, USA

This paper proposes two methods for computing confidence intervals with exact or conservative coverage following a group sequential test in which an adaptive design change is made one or more times over the course of the trial. The key idea, due to Muller and Schafer (2001), is that by preserving the null unconditional rejection probability of the remainder of the trial at the time of each adaptive change, the overall type I error, taken unconditionally over all possible design modifications, is also preserved. This idea is further extended by considering the dual tests of repeated confidence intervals (Jennison and Turnbull, 1989) and of stage-wise adjusted confidence intervals (Tsaiats, Rosner and Mehta, 1984). The method extends to the computation of median unbiased point estimates.

http://ctj.sagepub.com
ADJUSTMENT ON THE TYPE I ERROR RATE FOR A CLINICAL TRIAL THAT MONITORS FOR INTERMEDIATE AND PRIMARY ENDPOINTS
Susan Halabi, Kouroso Owzar and Christian Kappeler
Duke University, Durham, North Carolina, USA

In many clinical trials, a single primary endpoint is the basis of the monitoring. Many trials are lengthy in duration and investigators are often interested in using an intermediate endpoint for consideration for an accelerated approval, but will rely on the primary endpoint (such as overall survival) for the full approval. We consider a clinical design where both the intermediate (progression-free survival) and the primary endpoint (overall survival) are used for monitoring the trial while preserving the overall global error rate at a specified nominal level. The proposed design is illustrated using a Prostate Cancer Trial as an example. To allow for dependence between the two endpoints, their joint distribution was generated using parametric copulas.

REALISTIC CONSIDERATIONS AND APPLICATIONS FOR COMPARATIVE CLINICAL TRIALS
Susan M. Geyer, Vera Suman and Morie Gertz
Mayo Clinic, Rochester, Minnesota, USA

Randomized phase III clinical trials are the standard when comparing efficacy endpoints between treatment groups. However, in rare disease settings and/or in trials where the treatment regimens to be compared are inherently very different, finding patients willing to participate in a randomized trial can be challenging at best. In this age of easy access to disease information from a multitude of sources including the internet, patients often come with specific ideas and preferences for their treatment. This phenomenon can be even more pronounced in the referral setting. There have been study designs proposed that allow for some of these patients who refuse to be randomized to select their own treatment, such as the comprehensive cohort design. We extend these proposals to accommodate the situation where virtually all patients will choose their own treatment, where the study is essentially a nonrandomized phase III trial. We propose a nested case control matching approach in this clinical trial setting as a means to still enable comparisons of the efficacy endpoints of interest. We discuss the pros and cons to nonrandomized phase III trials and the need to incorporate patient-reported outcome endpoints addressing patient-physician communication and decision-making as well as patient’s information-seeking behavior and their impact on participation in clinical trials.

IMPLEMENTING A SECOND RANDOMIZED TRIAL ENROLLING MID-STUDY TREATMENT FAILURES FROM THE FOCAL SEGMENTAL GLOMERULAR SCLEROSIS (FSGS) CLINICAL TRIAL
Jennifer J. Gassman¹, Howard Trachtman², Debbie Gipson², Aaron Friedman², Tom Greene², Suzanne Vento², Amber Thompson² and Leslie Powell²
¹Cleveland Clinic Foundation
Cleveland, Ohio, USA
²The Font Study Group

The FSGS Study, a multicenter NIH-funded randomized clinical trial, includes 2 to 42-year-old patients with steroid resistant FSGS and is testing whether cyclosporine (CSA) or mycophenolate mofetil (MMF) and oral dexamethasone pulses will cause FSGS to go into remission, defined by a specified reduction in the protein-to-creatinine ratio in a patient’s first morning urine. The categorical study outcome is assessed at weeks 26, 52, and 78. At week 26, patients who show no response to treatment reach a category of the primary outcome and are defined as early non-responders (treatment failures); their participation ends and other treatments can be tried. Patients who show some response remain on CSA or MMF until week 52, when remaining patients are categorized for the primary outcome; the main secondary outcome is whether remission is maintained until Week 78. Week 26 and Week 52 treatment failures are eligible for the FONT Study, an NIH-sponsored trial investigating a TNF-α antagonist (Adalimumab, Humira) and a PPAR γ agonist (Rosiglitazone, Avandia). In a Phased Innovation Award (the R21 Phase), the safety, tolerance, and pharmacokinetic profile of these novel therapies is under way.

Enrollment in the FSGS Study is challenging. FSGS is rare, and many prevalent patients are ineligible due to prior treatment with the study drugs. The FONT Study helps FSGS Study recruitment and patient/physician acceptance; at multiple FSGS Study sites, patients with treatment failure can continue to participate in research through the FONT Study. Recruitment in FONT is enhanced by entry of both those who failed on study treatments during the FSGS and those who failed these treatments before the onset of the FSGS Clinical Trial.
34
BEST OF FRIENDS: A LOOK AT THE RELATIONSHIP BETWEEN THE BIOSTATISTICIAN AND DATA MANAGER FOR COLLECTING QUALITY DATA
Nicole C. Close and Lori Ovington
US Army Medical Research and Material Command, Fort Detrick, Maryland, USA

Before and during a clinical trial, a significant amount of time is spent ensuring quality of the trial's data. One of the most important relationships within the project team for this function is that of the trial's Biostatistician and the Data Manager (DM). The collaboration and communication between these individuals is crucial. Key areas in which the Biostatistician and the Data Manager works closely together is in protocol development and review, case report forms (CRFs), tables and listings, validation processes, and the final study report.

A sample of best practices in these key areas include for the Biostatistician to:
• provide second review to the DM in reviewing the study events table to the visit schedule to ensure completeness
• help DM understand how subjects will be analyzed and how and what data are required when early withdrawal and/or drop-out occurs,
• assist the DM, as a united front, in paring down the CRFs to only collect the data needed for the analysis,
• make sure that primary and secondary endpoints are captured and checked correctly on the CRFs,
• review with the DM necessary data for subjects who have early withdrawal or drop-out,
• review data pre-lock as the review will have a different angle from the DMs review, and
• work closely to document any discrepant findings in the locked database that will not be corrected.

The Biostatistician and the DM's relationship is an imperative. Through best practices, open communication and a partnership prior and during the trial, quality and well reviewed data will be collected and used in the analysis.

35
UNSCHEDULED INTERIM ANALYSIS DUE TO UNDERENROLLMENT IN A “SEASONAL” PEDIATRIC STUDY
Richard Holubkov, Stacey Knight, J. Michael Dean, Nathan Kuppermann and Howard Corneli for the PECARN Investigators, University of Utah, Salt Lake City, Utah, USA

The federally funded Pediatric Emergency Care Applied Research Network (PECARN) carried out a multicenter, double-masked, placebo-controlled study of steroids (dexamethasone), given to infants presenting with bronchiolitis in the emergency department (ED). Investigators at the 21 nationwide EDs expected to enroll 770 subjects during the 2003–04 winter bronchiolitis “season”. However, following delayed startup and a relatively mild season, only 213 were enrolled at the first season’s end. The DSMB, initially charged solely with safety review, deliberated stopping rules for an unscheduled interim analysis prior to reviewing first-season data. Advocates of a liberal, Pocock-type monitoring boundary noted responsibility to release positive findings before the next bronchiolitis season, and that limited PECARN resources could be shifted if stopping occurred. Supporters of more conservative (O'Brien-Fleming, Haybittle-Peto) stopping rules noted that when presented to the pediatric community, results from this unique RCT should be unequivocal, maximizing statistical power overall and for key subgroups. The compromise was a Haybittle-Peto rule with stopping boundary corresponding to $p < 0.01$, preferred by clinicians over O'Brien-Fleming due to conceptual simplicity. Futility stopping boundaries were not implemented. After first-season data review, the DSMB recommended study continuation, with no additional interim looks for efficacy. Recruitment ended (final n = 600) after two additional seasons and without knowledge of interim analysis findings, due to practical and cost concerns.

A prespecified, detailed monitoring plan (“to be used if enrollment is unexpectedly low”) in the original DSMB charter would have streamlined interim DSMB activities. In “seasonal” study settings, where continuation for an additional season implies personnel downtime and extended delay in reporting final results, optimal DSMB monitoring strategies may differ from continuous enrollment scenarios.

36
MODIFYING PRACTICES TO MEET AMBITIOUS SPONSOR TIMELINES
Leah V. Passmore, Frank Leus, Laurie Russell, Karin Nijssen, Connie Sharpe, Charles Tegeler, Gregory W. Evans and Michiel Bots
Wake Forest University School of Medicine, Winston Salem, North Carolina, USA

The Division of Public Health Sciences at Wake Forest University School of Medicine serves as the Data Management Center (DMC) for data from two B-mode ultrasound core laboratories involved in a pair of industry sponsored, international phase III randomized clinical trials. There is a local core laboratory at WFU as well as one located at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht. Each laboratory is responsible for managing and reading participant ultrasound scans. The DMC has created a data management system (DMS) validated in compliance with 21CFR Part 11. The DMS is designed to receive, manage and validate data from the core laboratories and subsequently transfer study data to the sponsor.
The sponsor’s intent was to present the study results four months after the last participant visit. Therefore, the DMC was given a schedule allowing only one month between the last participant visit and the final data transfer to the sponsor. In this interval, final participant scans were received and read by the core labs, reading data was uploaded to the DMC, and all data queries were addressed, including between visit queries that could not be generated until final participant visits were received. This implied that over 11,000 records for more than 1600 participants had to be locked as final within one month of the last subject visit. To reach this ambitious deadline, modifications were made to study related practices at both core laboratories and the DMC. This presentation will outline some of the obstacles encountered in reaching such deadlines, solutions implemented, and our achieved performance compared to predefined benchmarks.

37
COSTING MODEL FOR PUBLICLY FUNDED NON-DRUG RANDOMISED CONTROLLED TRIALS
John D. Norrie, Alison McDonald and Gladys McPherson
University of Aberdeen, Aberdeen, UK

There have been major changes in the environment in which publicly funded randomised controlled trials are conducted in the last 5 years. Ethical, legal, financial, and scientific oversight have all been tightened, aiming to increase the quality of trials and so ensuring both the safety of participants and protecting the investment of tax payers money. These developments have presented challenges for the funders, with the notional cost of a trial increasing without a corresponding uplift in overall funding budget. Funders have naturally looked harder for convincing evidence that trial proposals represent value for money. This in turn has led to academic triallists needing to develop transparent, evidence based “Costing Models” to justify their resource requests. The Centre for Healthcare Randomised Trials (CHA RT) in the Health Services Research Unit (HSRU), Aberdeen University, has a reputation for designing and conducting high quality publicly funded trials of principally non-drug technologies. Its portfolio typically comprises 10 ongoing long term large scale trials, with individual trials funded between $1 m to >$5 m. This talk describes the development of CHaRT’s Costing Model, indicating how a new protocol is processed through the Costing Model to give resource requirements for the core competencies (such as statisticians, trial managers, IT professionals, health economists) at a trials support unit, and at recruiting centres (such as clinical investigators and study co-ordinators) or ancillary sites (such as hospital laboratories). Algorithms for non-staff costs including (a) models for per participant payment and (b) resources for Steering and Data Monitoring Committees, and (c) patient and study personnel travel are discussed. The CHaRT Costing Model has been developed from evaluation of the historical portfolio of HSRU/CHaRT trials over the last decade, and in this presentation the emphasis is on the generic features and methodology that would make the approach applicable to a wide variety of settings.

38
A CLINICAL TRIALS CONSULTANCY SERVICE AT THE UNIVERSITY MEDICAL CENTER FREIBURG (GERMANY)
Gabriele Ihorst, Erika Graf, Birgit Grotejohann, Andreas Zaehringer and Herbert Maier-Lenz
University Medical Center Freiburg, Freiburg, Germany

The Center The Center of Clinical Trials (CCT; Zentrum Klinische Studien) is a central department of University Medical Center Freiburg. As a center of competence, it offers comprehensive services for clinical trials, covering planning, initiation, conduct and evaluation of studies. The CCT has set itself the objective of ensuring that patients benefit from medical progress by improving the quality of clinical trials and increasing the acceptance of clinical research in academic circles. A team consisting of healthcare professionals, biostatisticians, data managers, project managers, study nurses, monitors and quality managers works closely together at the CCT to achieve these objectives.

Consultancy service CCT offers comprehensive consultancy for the planning of clinical projects to the medical community of the University Medical Center. For clinical trials under German Drug Law the advisory service is strongly recommended by the Board of Directors of the University Medical Center Freiburg and the Medical Faculty before submission of the protocol to the University ethics committee. However, the service is offered also for clinical trials on medical devices and for diagnostic, prognostic or epidemiological studies, both in industry-sponsored and in scientific investigator initiated settings. Consulting refers to regulatory, logistical, methodological and financial aspects of the project and is performed by a medical professional, a project manager and a biostatistician. Investigators send the study protocol or study outline for review to the CCT team. In many cases counseling takes place in a meeting. Finally, recommendations are given in writing. Between September 2005 and August 2006, advice was given for 98 projects, 58 of them investigator initiated.

Conclusion Among the manifold other CCT activities in professional training, the consultancy service offers an invaluable opportunity to enhance the planning quality especially for investigator initiated trials and thus to promote state-of-the-art research in accordance with international quality standards of Good Clinical Practice (ICH-GCP).
39
RECRUITMENT STRATEGIES TARGETTED TO THE END OF A TRIAL
Laura Tomat, Kellie Murphy, Sheila Hewson and B. Anthony Armson
University of Toronto, Toronto, Canada

MIRU is the coordinating centre for international, multi-centre randomized control studies. One of these studies, MACS (Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study), has 80 participating centres in 20 countries. The primary research question is, for women who are at increased risk of preterm birth, do multiple courses of antenatal corticosteroid, every 14 days, decrease (or increase) the risk of neonatal mortality or significant neonatal morbidity, compared to placebo? As the four year enrollment period for MACS drew to its close, it became evident that the study would not meet its recruitment targets. Though additional funding allowed for an extension to recruitment, new and extraordinary strategies were needed to reach the recruitment goal.

The first step involved identifying why recruitment was behind target. The two main factors identified were trial fatigue and communication barriers due to language, time and distance constraints. Addressing the problem of trial fatigue required re-introducing enthusiasm at the sites. This paper will share the approaches used to motivate and communicate with our sites with the goal of spreading excitement into 20 countries and re-establishing the MACS profile at the participating centres. While communication was a main tool used to address recruitment fatigue, it was also recognized as a barrier. This paper will describe how lead investigators from various countries were invited to meet face-to-face and work towards overcoming this challenge.

The strategies employed increased the recruitment rate by 59%. Although these strategies could not be employed throughout the duration of the trial due to their intense resource requirements, with a specified deadline, key collaborations, and contagious enthusiasm for a contained period, the recruitment strategies worked.

40
ASSESSING THE CONTRIBUTION OF LATE STARTING SITES IN RANDOMISED CONTROLLED TRIALS
Kathrin Stoll1, Anthony Armson2 and Eileen K. Hutton1
1University of British Columbia, Vancouver, Canada
2University of Toronto, Toronto, Ontario, Canada
3McMaster University, Hamilton, Ontario, Canada

A recent study of recruitment patterns in multicentered randomized controlled trials (RCT) reported that recruitment centers that become active within 5 months from the time the first patient is randomized are responsible for 90% of total enrollment in the trial. Based on these results the authors concluded that late starting sites do not contribute significantly to overall recruitment, and questioned the protracted effort required to attract new sites. We were interested in determining if these findings applied to multicentered RCTs conducted at our trial unit. We attempted to replicate the findings using 163 trial centers from three multi-center trials coordinated at The Maternal Infant and Reproductive Health Research Unit: Twin Birth Study, Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study and Early External Cephalic Version 2 Trial. For each center we determined the time interval between the first patient entry in the trial and at each site. We then recoded this variable into sites that recruited within 5 months of the first entry into the trial and centers that recruited after 5 months. Using a correlational analysis and t-test preliminary results indicate significantly less deviation from recruitment goals amongst late starting sites (r = 0.47; p = 0.001 and t = −2.51; p = 0.02). In addition early starter sites enrolled 52% (22%) of overall recruits (N = 2400) compared with 1877 (78%) of late starter sites.

Our results did not replicate those of the prior research. In fact we observed that late starting sites make a more significant contribution to recruitment than early starting sites. Our paper investigates these divergent results in more detail and explores other cut off points to delineate early from late starter sites.

41
FACTORS AFFECTING PARTICIPATION IN THE CLINICAL EXAMINATION PHASE OF A TWO-STEP GENETIC SCREENING STUDY
Leah V. Passmore, Mark Speechley, David M. Reboussin, James C. Barton, Helen Harrison, Lari Wenzel, Charles A. Rivers, Margaret Fadojutimi-Akinsiku, Emily L. Harris and Sharmin Diaz
Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA

The Hemochromatosis and Iron Overload Screening (HEIRS) Study is an racially and ethnically diverse, primary care-based screening study for hemochromatosis and iron overload conducted at five Field Centers in the US and Canada. HEIRS Study had two principal phases: initial screening and clinical examination. 101,168 primary care patients were screened between February 2001 and March 2003. Initial screening results identified 2256 participants with high serum iron measures or HFE C282Y homozygosity, and 1232 controls eligible for a Comprehensive Clinical Exam (CCE). Eligible participants were invited by letter to attend the CCE. Of those invited, 74% of the positive screens and 52% of the controls attended the CCE. We examined potential explanatory
factors affecting retention for both screen positives and controls. Such factors were drawn from initial screening data and included: age, gender, race/ethnicity, preferred language, Field Center, self-reported diagnoses for chronic conditions sometimes associated with iron overload, self-rated physical and psychological well-being, and attitudes about genetic testing and the perceived role of lifestyle in health. We found that both screen positives and controls were less likely to participate if under the age of 45, recruited at non-HMO Field Centers, or non-Caucasian. Among screen positives, women participated at a higher rate than men. Such assessments of differences between those who did and did not attend will be presented. We will discuss the implications of differential participation in a two-stage study.

**42**

RECRUITMENT TO PUBLICLY FUNDED SURGICAL RANDOMISED CONTROLLED TRIALS

Jonathan A. Cook, Craig Ramsay and John Norrie
University of Aberdeen, Aberdeen, UK

A recent review showed that only about 30% of the trials funded by the UK Medical Research Council and the NHS Health Technology Assessment Programme recruited as expected. Recruitment in surgical trials has been noted to be particularly difficult. One reason for this is that recruitment is constrained by availability of resources which results in delays in treatment. Secondly, it can be difficult to randomise participants immediately prior to surgery. Comparisons of surgical versus medical treatments are particularly susceptible to both of these issues. These problems are further compounded when the study is multi-centre: there is some evidence to suggest that new centres often fail to recruit at the same level as early centres. Initial recruitment calculations are often based upon expert opinion informed by limited empirical evidence. Ongoing assessments of recruitment performance in many surgical trials are not rigorous or statistically based and are often the product of simplistic or selective extrapolations of the data which can be misleadingly alarmist or falsely reassuring.

A modeling approach would allow the natural adjustment of expected recruitment as the trial progresses based on the accumulating evidence within a trial. Such a model would allow the continual updating of predictions to achieve recruitment conditional on the current status, as the trial progressed. This presentation will use the recruitment details from a set of surgical trials to identify key timepoints during the life of a trial. Difference between centres and delays due to limited availability of resources, a waiting list effect, will be considered as well the impact of shock events such as internal centre factors which prevent recruitment for a short period of time (for example, an outbreak of MRSA).

**43**

CONDUCTING A CLINICAL TRIAL OF ADOLESCENTS IN A HIGH SCHOOL SETTING: CHALLENGES AND SOLUTIONS

Rosemary A. Hollick, Angela Badcon and Lee H. Harrison
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Recognition of the need for more clinical trials to evaluate the effects of drugs and biologics among adolescents has heightened awareness of the special challenges posed when designing and conducting trials among this population. The “Evaluation of the Effect of Tetravalent Meningococcal Conjugate Vaccine on Serogroup-Specific Carriage of Neisseria meningitidis (Carriage) Study” is a randomized clinical trial to evaluate the effect of MCV4 vaccine on pharyngeal carriage of N. meningitidis among adolescents, a primary group of carriers of the organism. All students enrolled in grades 9 through 12 at four area high schools (N = 6,045) were eligible for participation; the target sample size was 2,200.

Challenges encountered include recruitment, obtaining informed consent (parents) and assent (students), and conducting the trial within a high school setting. Initial recruitment efforts, primarily parent-directed, yielded 700 enrollees. Intensive, student-focused recruitment efforts were then undertaken, which, in conjunction with a spurt in enrollment following each school’s first study day, boosted enrollment to 1,406 students. Study consents and assents were mailed; 14.3% of the consents and 11.8% of the assents returned contained incomplete or inconsistent information. Strategies were developed to correct these problems expeditiously so that the students affected could participate in the trial.

Finally, adjustments were made to study activities to accommodate school hours and students’ schedules, to accurately identify enrolled students, to limit time out of class, and to maximize study day attendance. Challenges and solutions encountered in this trial are applicable to other efforts utilizing adolescents. The myriad of unique issues presented by clinical trials of adolescents need further investigation.
CANADIAN VS. US RECRUITMENT IN MULTICENTER NIH STROKE PREVENTION CLINICAL TRIALS:
ARE CANADIAN SITES THAT MUCH BETTER?
Virginia J. Howard, Marie McClelland, Annette Hache, Anne Doherty,
Mary Wilcox, Elizabeth G. Sides, Jason Avery and Alice J. Sheffet
University of Alabama at Birmingham and Medical University of South Carolina,
Birmingham, Alabama, USA


Cumulatively, Canadian sites comprised 14% of sites but recruited 30% of the patients. Canadian recruitment was above expected in each trial (1.30–2.86 times). In ACAS, 3 of the 4 Canadian sites were in the top 10 in recruitment; in NASCET, 6 of the 15 sites were in the top 10, and in VISP, of the top 10 sites, 7 were Canadian. While Canadian sites were added later in CREST, already 2 of the 6 Canadian sites are in 3rd and 4th place. Centralization of the medical system in Canada may play a significant role in efficiency of the screening and enrollment processes for clinical trials, an advantage that should be considered in site selection.

### Table: Recruitment in Multicenter NIH Stroke Prevention Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Total Recruitment</th>
<th>Canadian Recruitment N (%)</th>
<th>Total Sites</th>
<th>Number of Canadian Sites N (%)</th>
<th>Ratio of Canadian % Recruitment / % Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAS</td>
<td>1662</td>
<td>221 (13%)</td>
<td>39</td>
<td>4 (10%)</td>
<td>1.30</td>
</tr>
<tr>
<td>NASCET</td>
<td>2929</td>
<td>1182 (40%)</td>
<td>106</td>
<td>15 (14%)</td>
<td>2.86</td>
</tr>
<tr>
<td>ACE</td>
<td>2849</td>
<td>1207 (42%)</td>
<td>74</td>
<td>19 (26%)</td>
<td>1.62</td>
</tr>
<tr>
<td>VISP</td>
<td>3680</td>
<td>1037 (28%)</td>
<td>56</td>
<td>10 (18%)</td>
<td>1.56</td>
</tr>
<tr>
<td>CREST*</td>
<td>1463</td>
<td>133 (9%)</td>
<td>100</td>
<td>6 (6%)</td>
<td>1.50</td>
</tr>
<tr>
<td>ALL</td>
<td>12583</td>
<td>3780 (30%)</td>
<td>375</td>
<td>54 (14%)</td>
<td>2.14</td>
</tr>
</tbody>
</table>

(*as of 11/21/06)

ASSESSING CAPACITY TO GIVE INFORMED CONSENT IN OUTPATIENTS WITH MILD-TO-MODERATE ALZHEIMER’S DISEASE
Peter D. Guarino, Susan Love and Maurice Dysken
Dept. of Veterans Affairs, West Haven, Connecticut, USA
VA Medical Center, Minneapolis, Minnesota, USA

**Background** Informed consent requires that a study volunteer understands the purpose, procedures, and the risks and benefits of the study, and agrees, without coercion, to participate in the study. Outpatients with mild-to-moderate Alzheimer’s disease (AD) may lack decisional capacity or have diminished autonomy. While there is no consensus on how to reliably assess autonomy or decision-making capacity in this group of patients, studies that have trained researchers to use standardized questions on key domains of decisional capacity have produced valid results with good inter-rater reliability.

**Objective** The objective of this study is to further develop an instrument that can be used to assess capacity to give informed consent.

**Methods** A 16-question assessment of capacity to give informed consent was developed that queries potential research participants on the content of the informed consent document and their self-reported understanding. This questionnaire was approved by the Minneapolis VAMC IRB to assess capacity in AD patients who were eligible for an industry-sponsored clinical trial. To be considered capable of giving informed consent, patients were required to answer at least 70% of the first 10 questions; in addition, all three of questions 11–13 had to be answered correctly because the information contained in these questions was considered essential to having the capacity to consent. The final 3 questions were based on a validated scale to assess perceived understanding.

**Results** Only 2 of the first 7 patients entering the trial were judged to have capacity. For these 7 patients there was no relationship between the MMSE score (mean: 21.9; range: 16–26) and capacity to consent. The mean MMSE scores = 20.5 for those with capacity and 22.4 for those without (p = 0.58). The data do appear to suggest a possible relationship between perceived understanding and capacity (p = 0.09) with a significant association between perceived understanding and the percent correct on the 3 required questions (p = 0.002).

**Conclusions** MMSE appears to be a poor predictor of capacity as judged by a questionnaire that quizzes patients on important elements of a study to which they are consenting. The relationship between perceived understanding and capacity appears to be much stronger. Although most clinical trials in AD patients with mild-to-moderate dementia do not require an assessment of capacity, this practice is likely to change since many, and perhaps most,
of these patients lack capacity to give informed consent. More research is needed on how best to assess capacity in AD and other vulnerable populations. VA Cooperative Study #546, a trial in 840 AD patients that will launch in 2007, will use similar methodology to assess capacity and its relationship to understanding and cognitive function.

46
AN ONLINE APPLICATION FOR TRACKING AND IMPLEMENTING SPECIMEN CONSENT CHOICES FOR CLINICAL TRIALS: A GYNECOLOGIC ONCOLOGY GROUP INITIATIVE
William E. Elgie1, Kathleen Darcy1, Zoe Miner1 and Stephen Qualman2
1Roswell Park Cancer Institute, Buffalo, New York USA
2Children’s Hospital, Columbus Ohio, USA

**Background** Specimen requirements are incorporated into clinical trials across study types and disease sites at an increasing rate. The consent document for this type of trial has become more complicated and individual questions are often embedded asking the patient for specific per-mission to allow their specimens to be submitted and used for a specific reason such as the clinical trial, future cancer research, future non-cancer research or genetic testing. Based on the volume and complexity of the information that must be track to honor the rights, wishes and confidentiality of our participants, a manual process is no longer efficient or accurate. An online application needed to be developed for the Gynecologic Oncology Group (GOG) to track and implement specimen consent choices electronically.

**Method** A web-based application was developed that allows real-time entry and unlimited amendments to specimen consent choices for up to 10 unique questions embedded into a consent document for a given GOG clinical trial. The application also has layers for management, reporting and notification that will trigger manual confirmation with participating institution regarding requests for immediate specimen destruction and validation with the GOG Tissue Bank that specimens have been destroyed.

**Results** Between 2002 and 2006, over 42,000 consent choices have been registered for over 10,000 people for 39 clinical trials and electronically transferred to the GOG Tissue Bank in Columbus Ohio and the GOG Statistical and Data Center. Thus far, 861 patient entries indicate restrictions on the use of their specimens, and over a dozen people have requested immediate destruction of their specimens.

**Conclusions** An online application was developed that efficiently and accurately tracks and implements specimen consent choices for clinical trials in an international multi-institutional setting.

47
SHOULD ATTRIBUTION BE CONSIDERED WHEN INTERPRETING ADVERSE EVENT DATA: AN EVALUATION OF PHASE III PLACEBO CONTROLLED CANCER CLINICAL TRIALS
Daniel Sargent, Shauna Hillman, Brian Bot and Sumithra Mandrekar
Mayo Clinic, Rochester, Minnesota, USA

**Background** Since March 1998, the Common Toxicity Criteria version 2.0 (CTC) has been required for collecting adverse event data in US National Cancer Institute sponsored clinical trials. The CTC requires the collection and reporting of attribution of adverse events to study treatment. Collection and reporting of attribution adds time and cost to the clinical trial process. We investigate whether attribution adds value to the interpretation of AE data.

**Methods** Patients on the placebo arm of 2 randomized phase III clinical trials (one in patients with advanced lung cancer, one in patients with gastrointestinal stromal tumors (GIST)) were chosen since the true relationship of the event to study treatment is known (“unrelated”). Attribution was collected per CTCv2.0 and categorized as “not related” (not related or unlikely) and “related” (possible, probable, or definite). Results: On the lung cancer trial, 84 patients experienced a total of 1013 AEs. 47% of AEs were reported as “related” with 36% as possibly related. ‘Known’ AEs (specified per protocol) were more likely to be reported as “related” (p = 0.005). Pulmonary AEs were more likely to be reported as “not related” (p = 0.0006). No patterns were observed by gender, age, PS, severity or treatment cycle of AE. When the same event was reported on the same patient in multiple cycles, the attribution category changed at least once 36% of the time with 25% changing from “related” to “unrelated” or vice versa. Similar findings were observed in the GIST trial.

**Conclusion** Almost 50% of events from the placebo arms of two phase III cancer clinical trials were reported as being attributed to study treatment, and 25% of the time the same event was not consistently attributed. These data suggest that attribution is difficult to determine, unreliable, and thus its value in large phase III trials is questionable.

48
PARENTAL DECISIONS TO DECLINE PARTICIPATION IN A NEONATAL TRIAL: AN EXPLORATION OF UNIFORMED REFUSAL
Claire Snowdon
London School of Hygiene and Tropical Medicine London, UK

**Background** Much empirical effort has been directed towards understanding decisions that people make about RCT participation. Whilst research describing attitudes and experiences of those accepting participation has...
grown in its range of focus and methodological sophistication, the experience of refusal is rarely considered outside the need to improve trial recruitment rates. We know little about how individuals who decline participation see, understand and experience their link to RCTs.

**Aim** To explore parental accounts of their decisions to refuse participation in a neonatal trial.

**Methods:** Detailed analysis of interviews with five parents who declined to enroll their baby into a UK neonatal trial. The interviews were taken from a large qualitative study involving interviews with 78 parents and 52 clinicians. The trial compared two clinically effective forms of surfactant and considered differential cost implications of their use for babies born 25–30 weeks gestation.

**Results** Parents expressed unease, mistrust and anger. There were major gaps in their knowledge; none was aware of what the trial interventions were but all perceived them as new and unnecessary. They saw a clinical situation devoid of therapeutic or protective intent, where a preterm baby may be placed at risk for experimental purposes. All felt that their refusal to participate was crucial to their baby’s survival.

**Conclusions** This exploratory research suggests particular ways in which parents might be left with inadequate and distorted information - in such situations informed refusal is not achieved. Further research is needed to see whether these findings are replicated with larger numbers in other settings.

**49**

**PROMOTING POLICY RELEVANT TRIALS: THE SUPPORT COLLABORATION**

Marion K. Campbell, Andy Oxman, Edgardo Abalos, Carl Lombard, Eduardo Bergel and Dave Sackett  
University of Aberdeen, Aberdeen, Scotland

Access to, and use of, reliable evidence of the effects of interventions is essential to evidence-informed decision-making. Across the world, however, a substantial proportion of the available health budget is used for the implementation of interventions whose effectiveness is unknown or even disproved. The consequences of this inappropriate use of resources are particularly problematic in low and middle income countries (LMICs) where guidance on the optimal use of the limited resources available would be particularly beneficial.

Against this background, the EU recently funded a €2m international collaboration (the SUPPORT collaboration) to support the development and use of policy relevant trials, with a focus on maternal and child health (issues of particular relevance to LMICs). The members of this collaboration include clinicians and researchers from Europe, Africa and South America. It builds on a previous successful collaboration (the PRACTIHC collaboration) which developed tools for the design of pragmatic trials. The aim of SUPPORT is to improve the use of reliable evidence in policy and management decisions through the delivery of a number of work packages, including: development of guidance on the preparation of summaries of best evidence in a way that is easily accessible to decision makers; development of tools to support access to research evidence; development of tools to support the conduct of pragmatic trials; development of tools to facilitate funding of trials; training of decision makers in the use of research evidence and the management of change; and training for trialists. This presentation will outline how such multi-national collaborations can be configured and how efficiencies can be gained from cross-continental linkages. It will also describe the outputs from the work packages currently underway.

**50**

**ALTERNATIVE IRB MODELS FOR MULTICENTER CLINICAL TRIALS: CURRENT STRATEGIES AND ONGOING CHALLENGES**

Ann Ervin, Curtis Meinert and Susan Tonascia  
Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

Institutional Review Boards (IRBs) were established at time when single-center, investigator-initiated research predominated. In 1973, multicenter clinical trials represented less than 1% of all clinical trials, but currently more than 14% include two or more clinical centers. Multicenter trials are subjected to repetitive IRB review at the local level, potentially resulting in disparate requirements for consent forms, increased expenditures, and delays in the commencement of research activities. Some institutions establish alternative IRB models to designate a single IRB to review the protocol for participating clinical centers, to share review responsibilities, or to share resources (e.g., consent documents, IRB meeting minutes). These arrangements are thought to facilitate the review process, but estimates of their utilization in the United States and empirical comparisons to other methods of review are limited.

The objectives of this research were 1) to characterize multicenter-specific IRB procedures and requirements, including the use of alternative IRB review models and 2) to examine the characteristics of written institutional agreements to conduct cooperative IRB review in the multicenter setting.

Of the 126 US medical and public health IRB systems included in the sample, 66 (52%) engaged in an alternative IRB arrangement. Intra-institutional IRBs (9%), commercial IRBs (81%), hospital IRBs (43%) and governmental IRBs (57%) were listed as cooperating entities. IRB systems varied appreciably in their adoption of multicenter-specific submission requirements; included were requests for clinical center contact information (37%), IRB approval letters (29%), and IRB contact information (8%).

We will present additional findings from our review of 126 US medical and public health IRB systems and discuss ethical and practical considerations for trialists contemplating alternative IRB models.

http://ctj.sagepub.com
CODING OF CLINICAL TRIALS AND SYSTEMATIC REVIEWS IN THE COCHRANE LIBRARY USING INTERNATIONAL STANDARDS

Stephen Gichuhi, Barbara Hawkins and Kay Dickersin
The Johns Hopkins University Bloomberg School of Public Health
Baltimore, Maryland, USA

Registers and databases of reports of clinical trials and systematic reviews are invaluable resources for clinical trialists, health professionals, and consumers. However, their utility in retrieval of information about a particular health condition and/or intervention is limited by variations in terminology used by different medical specialties and researchers. Coding clinical trials and systematic reviews using international coding standards in common use may improve access to and translation of evidence to practice. WHO’s International Classification of Diseases (ICD-10) is used internationally across research and clinical settings and presents a good option. The International Classification of Health Interventions (ICHI) is in beta testing prior to public release and would add additional indexing information.

The Cochrane Library currently includes 4,539 systematic reviews and review protocols and over 470,000 citations to controlled trials. The Library is searched using textwords and MeSH. A project is underway within the Cochrane Eyes and Vision Group (CEVG) to tag vision-related systematic reviews and over 7,000 clinical trials available to the public on The Cochrane Library, with ICD codes for (a) the disease entity(ties) addressed and (b) the intervention(s) evaluated. We present the results of the pilot study.

In our pilot study, two independent reviewers completed coding for 43 CEVG systematic reviews published in The Cochrane Library. Inter-observer agreement using ICD-10 was 81.4%. ICHI was suboptimal for coding of individual medications.

In the next phase of piloting, we will code a subset of trials and compare search results using the current MeSH and textword approach versus the new ICD coding.

Support by NIH contract NO1-EY-2-1003, National Eye Institute, National Institutes of Health

INCENTIVISATION OF PARTICIPANTS TO IMPROVE RESPONSE FOR PATIENT REPORTED OUTCOMES IN PUBLICLY-FUNDED RANDOMISED CONTROLLED TRIALS

Alison McDonald, John Norrie and Gladys McPherson
University of Aberdeen, Aberdeen, Scotland

Trials which rely on participant reported outcomes, often measured a long time after the intervention under experiment has been completed, routinely experience sub-optimal response from participants. Such missing outcome data can cause bias and loss of precision in estimating the effect of the intervention.

Three recent reviews have examined the evidence for various strategies for “incentivising” participants to improve response rates to postal questionnaires. One review suggested the use of incentives, particularly monetary, has a powerful effect on response rates to postal questionnaires while another indicated that there is a lack of evidence to suggest that incentives are useful in the context of health care research and that further evaluation is required.

The Centre for Healthcare Randomised Trials (CHaRT) typically runs a portfolio of approximately 10 large scale, long-term, publicly-funded, non-drug randomized controlled trials, nearly all with patient reported primary outcomes. CHaRT is therefore ideally placed to test the impact of these strategies by randomly allocating a broad range of incentives in such a way that no individual trial is over exposed to ineffective strategies, evidence of effectiveness is gained over a wide range of clinical conditions, and there is an opportunity to use adaptive design methodology to identify the most promising strategies and trial them against one another as the studies progress.

This presentation will review the current evidence and examine some of the controversies surrounding incentivisation (in particular ethical issues). The “Incentivisation Randomisation Experiment” [IRE] that CHaRT is undertaking in which we prospectively test the efficacy of the evidence based interventions, will be discussed.

FIXED AND RANDOM EFFECTS META-ANALYSIS – LET’S MEET IN THE MIDDLE!

Kristian Thorlund
Copenhagen University Hospital
Copenhagen, Denmark

Background Many authors of systematic reviews struggle with the decision of choosing between the fixed- and random-effects model. Both models possess pros and cons opposite of one another and often yield contradicting results. Seemingly, there is a need for a more refined approach that adopts the pros and minimises the cons concomitant of both models. Biggerstaff and Tweedie have proposed a random-effects approach that incorporates the precisions of the individual trials, and the variability of the between-study variance when calculating the trial weights. Presumably this method lets the fixed- and random-effects models ‘meet in the middle’, but the potential superiority of the model is yet to be evaluated.

Clinical Trials 2007; 4: 371–455 http://ctj.sagepub.com
Can Sequential Monitoring Boundaries Reduce Spurious Inferences from Meta-Analyses?

Copenhagen University Hospital, Copenhagen, Denmark
McMaster University, Hamilton, Ontario, Canada
University of Ioannina, Ioannina, Greece

Background There is a risk that results from apparently conclusive meta-analyses may be false. A limited number of events from a few small trials and the presence of random error may be under-recognized sources of spurious findings. Sample size requirement for a reliable and conclusive meta-analysis should be no less rigorous than that of a single optimally-powered randomized controlled trial. If a meta-analysis is evaluated before reaching a required sample size it should be evaluated in a manner that accounts for the increased risk that the result may represent a chance finding.

Methods We analyzed 33 meta-analyses in excess of a required sample size to detect a realistic treatment effect. We successively monitored the results of the meta-analyses by generating cumulative interim meta-analyses after each included trial. We performed sequential monitoring using both two-sided O'Brien-Fleming monitoring boundaries and the conventional criterion (p < 0.05) to evaluate statistical significance after each interim meta-analysis. We examined the proportion of false positive results and clinically important overestimates of treatment effects that resulted from the two approaches.

Findings False positive interim results were observed in 3 of 12 non-significant meta-analyses. The monitoring boundaries eliminated all false positives. Clinically important overestimates were observed 8 of 21 significant meta-analyses using the conventional criterion and in none using the monitoring boundaries.

Conclusion Evaluating statistical inference from sequential monitoring boundaries when meta-analyses fall short of a required sample size may reduce the risk false positive results and inflated effect sizes.

Randomized Controlled Trials Evaluating Stent for Vascular Diseases: A Systematic Review

Morgane Ethgen, Isabelle Boutron, Carine Roy and Philippe Ravaud
INSERM, Paris, France

Purpose To assess the quality of reporting of interventions, care providers and number of centers in randomized controlled trials assessing medical devices such as stents.

Data Sources MEDLINE and the Cochrane Central Register of Controlled Trials.

Data Extraction A standardized abstraction form was used to extract data.

Data Synthesis 85 articles were included. Details of the intended or actual interventions for the experimental group were reported respectively in 76 reports (90.5%) and in 62 reports (73.8%). In about 20% of the reports, no information was provided on the stents used. The number of centers was not reported in about one third of the reports. When reported, trials were mainly multicentric trials (n = 47; 55.3%). No data was retrieved about the volume of interventions performed in centers. Care providers' expertise was reported in only 2 articles. The quality of reporting was low as assessed by CLEAR NPT. The generation of allocation sequence was adequate between 89–94%, the fixed-effect model between 65–80%. In four of the six simulated meta-analysis scenarios the Biggerstaff and Tweedie approach initially had 3–5% lower coverage than the random-effects model, but converged to similar levels after 1–2 updates.

Conclusions Inadequate reporting on the management of the intervention, care providers and center may introduce bias in RCTs of stent intervention making their results questionable.
Abstracts

Clinical Trials 2007; 4: 371–455
http://ctj.sagepub.com

56
CHALLENGES OF ESTABLISHING A PUBLIC DATA SHARE WEB SITE
Cynthia L. Green, Jack Shostak and Jeng-Jong Pan
Duke Clinical Research Institute, Durham, North Carolina, USA

The National Institute on Drug Abuse (NIDA) established the National Drug Abuse Treatment Clinical Trials Network (CTN) to enhance the study and delivery of novel therapies and treatments for drug addiction to patients in community-based settings in an arena that had primarily been comprised of specialized research in restricted patient populations. The mission of the CTN is “to improve the quality of drug abuse treatment throughout the country using science as the vehicle.” To facilitate this mission, the CTN has established a public data share web site to collect and store study data and documentation for each completed CTN clinical trial. These data can be used for secondary efficacy and safety analyses or to design future trials. These types of analyses improve the quality of drug abuse treatment by increasing the scientific contribution of the original research.

Effective data sharing includes communicating to the research community that data are available, providing sufficient descriptive information regarding the data, enforcing compliance to standard semantics and structure, rendering the data in a usable format, making data accessible and protecting human subjects. We have been faced with many challenges, such as de-identifying the data, including the removal of variables such as site and race, as well as choosing a common data format to facilitate the pooling of data across trials. All original study data files are converted from their native format to a modified Study Data Tabulation Model (SDTM) standard format and made available on the web site as both SAS and ASCII files. This presentation will describe the factors that led to the choices we made and our experience in implementing the approaches chosen.

57
USING A PILOT TRIAL TO EVALUATE POTENTIAL PRIMARY OUTCOME MEASURES: RESULTS FROM THE LIFESTYLE INTERVENTIONS AND INDEPENDENCE FOR ELDERS (LIFE) STUDY GROUP
Mark A. Espeland1, Michael Miller1, Thomas M. Gill3, Jack Gurinik3, Roger Fielding3, Anne B. Newman5, Fang-Chi Hsu1, Michael Walkup1 and Marco Pahor6
1Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA
2Yale University School of Medicine, New Haven, Connecticut, USA
3National Institute on Aging, Bethesda, Maryland, USA
4Jean Mayer USDA Human Nutrition Research Center on Aging, Boston, Massachusetts, USA
5University of Pittsburgh, Pennsylvania, USA
6University of Florida, Gaines, Florida, USA

Pilot studies are often conducted to inform the development and design of major clinical trials. A common goal of these studies is to gain experience with several measures under consideration as primary outcomes for the main trial. For example, the LIFE pilot trial collected data on several potential measures of mobility disability, including ability to complete a 400 meter walk in <15 minutes, ability to complete a 4 meter walk in <10 seconds, a physical performance battery, and a self-reported disability questionnaire. Mobility disability, which is not directly measurable, was parameterized as a time-varying latent variable with changes expressed as random effects. The probability of failure in the two walk outcomes and the mean values of the performance battery and questionnaire were linked to this latent variable within a hierarchical model. A Gibbs sampling algorithm was used to fit longitudinal data from the 424 LIFE pilot trial participants to this model. Changes in all four measures were intercorrelated; however, the 400 meter walk outcome appeared to be most strongly associated with the construct of mobility disability: a 20% change in the probability of 400 meter walk failure was estimated to correspond to a mean change of 0.28 standard deviations in mobility disability. The posterior random effects distribution may be used to characterize how these changes vary among participants. Our results indicate that latent variable modeling applied to pilot study data can provide support in selecting among potential primary outcome measures.

58
MODELING CLUSTERED ODDS RATIO IN A CLINICAL TRIAL FAMILY STUDY – RELATIVE ODDS RATIO IN DCCT/EDIC GENETICS STUDY
Wanjie Sun, Patricia Cleary and John M. Lachin
George Washington University, Rockville, Maryland, USA

Many clinical trials explore familial association by supplemental measurements from first-degree relatives of probands randomized into a study. A common goal of these studies is to gain experience with several measures under consideration as primary outcomes for the main trial. For example, the LIFE pilot trial collected data on several potential measures of mobility disability, including ability to complete a 400 meter walk in <15 minutes, ability to complete a 4 meter walk in <10 seconds, a physical performance battery, and a self-reported disability questionnaire. Mobility disability, which is not directly measurable, was parameterized as a time-varying latent variable with changes expressed as random effects. The probability of failure in the two walk outcomes and the mean values of the performance battery and questionnaire were linked to this latent variable within a hierarchical model. A Gibbs sampling algorithm was used to fit longitudinal data from the 424 LIFE pilot trial participants to this model. Changes in all four measures were intercorrelated; however, the 400 meter walk outcome appeared to be most strongly associated with the construct of mobility disability: a 20% change in the probability of 400 meter walk failure was estimated to correspond to a mean change of 0.28 standard deviations in mobility disability. The posterior random effects distribution may be used to characterize how these changes vary among participants. Our results indicate that latent variable modeling applied to pilot study data can provide support in selecting among potential primary outcome measures.
and 5) second-order GEE, Alternative Logistic Regression (ALR) (Carey, Zeger and Diggle 1993). Simulation shows that ALR is the most consistent and efficient method of the five due to its full use of all sib pairs instead of using only (n-1) pairs as in the first 4 methods. And the efficiency improves with growing cluster size n. So besides the fact that ALR models the main effect (Y/X relationship) and association effect (OR/X relationship) simultaneously, it is also the most robust method of the five. DCCT/EDIC Genetics study was used as an example. Five methods were used to estimate sib-sib OR of diabetic nephropathy in EDIC/GENETICS among the 124 type 1 diabetic probands and 147 type 1 or 2 diabetic siblings. Relatives of affected probands had a 3 fold odds of getting diabetic nephropathy compared to those with unaffected probands. ALR was also applied to DCCT/FAMILY study to model father-child, mother-child and sib-sib OR simultaneously.

59
CONFIDENCE INTERVAL ESTIMATION WITH LOGNORMAL DATA: AN APPLICATION IN HEALTH ECONOMICS
Guangyong Zou
University of Western Ontario, London, Ontario, Canada

There has accumulated a large literature on the estimation of lognormal means owing to the fact that many data in scientific inquiries are positively skewed. Procedures have usually been proposed in a piecemeal fashion, with the approach based on numerical simulation of pivotal statistics emerging as the preferred one. As an alternative, we present a simple approach that requires only confidence limits available in introductory texts. Simulation results confirm the validity of our approach to constructing confidence limits for a single mean, a difference between two means, and a difference between two differences (net health benefit). Examples from previous studies are used to illustrate the methodology.

60
METHODS FOR THE ANALYSIS OF BOUNDED OUTCOME SCORES
Emmanuel Lesaffre and Marek Molas
Catholic University of Leuven, Leuven, Belgium

We review methods to analyze a response restricted to a finite interval, a so-called bounded outcome score (BOS). The distribution of a BOS can show peculiar shapes, like unimodal, U-, J- and inverted J-shape. Examples can be found in many research areas: compliance research (proportion of days that drug was taken correctly), in stroke trials using ADL scores like the Barthel index, pain studies using the visual analogue scale, etc.

In a two-group clinical trial (with or without correcting for baseline covariates) a popular approach is to use an ordinal regression model. An alternative approach is to assume a latent score on (0,1) with a logistic-normal distribution. Given the latent score, the observed BOS can be assumed to have a binomial distribution (in case it is a proportion) or it is a coarsened version of the latent score. We will compare the logistic-normal approach to the ordinal model. We show that the ordinal model is surprisingly efficient compared to our approach, but also that the ordinal approach gives a biased estimate of the treatment effect when the variance of the BOS depends on covariates. This is illustrated in a mathematical way and using a stroke trial (ECASS-I study, Lesaffre et al., 1993) comparing the effect of placebo and a thrombolytic agent on patients with an acute ischemic stroke.

For a longitudinal study with a BOS response, it is popular to use an ordinal random effects logistic/probit regression. However, this approach can lead to biasedly estimated treatment effects when the variance depends on covariates. We show that extending the logistic-normal approach to the repeated measurement case allows estimating the treatment effect unbiasedly. This is illustrated on a data set comparing the Barthel index at different visits between different revalidation centers on post-stroke patients.

61
APPROPRIATE METHODS FOR SPLIT-MOUTH STUDIES?
Emmanuel Lesaffre, Michael Vaeth and Sven Poulsen
Catholic University Leuven, Leuven, Belgium

In a split-mouth study, two or more dental treatments are randomly allocated to different sites of the mouth. A recent review (Lesaffre et al., 2006) showed that this technique is still quite popular in oral health research (especially in Europe), despite the potential problems with this design pointed out in a series of papers by Hujoel and co-workers about 10 years ago, namely: (1) biased estimate of treatment effect if carry-across is present; (2) less than expected efficiency; (3) practical recruitment problems, etc.

Firstly, we briefly review the quality of statistical analyses in split-mouth studies and focus how these papers dealt with the above mentioned problems. Secondly, we contrast the split-mouth design to the split-plot agriculture study and the classical cross-over design. Thirdly, modern approaches for the analysis of split-mouth studies will be reviewed, in the absence of carry-across effects. Fourthly, the critical remarks of Hujoel and co-workers will be critically re-examined in the presence of more advanced analysis techniques.
Two split-mouth studies will be taken for illustration. The first study compares two types of injections for mandibular nerve block in children. The second study compares the protective effect of an active and a placebo varnish on approximal caries in schoolchildren.

The conclusion is that the trial design is still difficult to analyze, despite the recent progress in statistical methodology. Some suggestions will be made to partially circumvent certain problems with this study design.

62
QUALITY-OF-LIFE ADJUSTMENTS ON MULTIPLE SCALES IN PATIENT SURVIVAL ANALYSIS
Adin-Cristian Andrei1 and Fernando J. Martinez2
1University of Wisconsin, Madison, Wisconsin, USA
2University of Michigan, Ann Arbor, Michigan, USA

In clinical trials, particularly those involving aggressive treatment strategies, close attention is paid to the patient health-related quality-of-life (HRQOL). Oftentimes, investigators are interested in both patient survival and HRQOL in connection to specific landmark events, such as disease episodes. The HRQOL-adjusted time-to-event (HRQOL-TTE) is a commonly used measure that provides a comprehensive approach for gaining additional insight into the synergistic aspects of the patient quantity/quality-of-life interplay. Existing methods for HRQOL-TTE only deal with situations where a single HRQOL measure is collected for each patient. However, there are numerous instances when multiple facets of patient's health status are simultaneously of high relevance for the medical investigator, in conjunction with overall survivorship. Using inverse probability of censoring weighting techniques, we propose and fully characterize an estimator for the joint distribution of several HRQOL-TTE. We then evaluate its performance in simulated settings and we illustrate its practical usefulness by presenting a National Emphysema Treatment Trial-related example.

63
OPERATIONAL, RECRUITMENT, AND TRAINING PRACTICES OF RESEARCH NETWORKS: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT
Paula Darby Lipman and Lauren Laimon
Westat, Rockville, Maryland, USA

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with members of a sub sample of CRNs to gather detailed information about the practices that each CRN employs to organize and conduct research.

Key findings from three of the survey modules will be presented. The Network Operations instrument examined site identification and recruitment policies and practices; study/protocol development and management; infrastructure support; and regulatory procedures. The Recruitment and Retention instrument explored network activities, procedures, strategies, and policies related to study planning, as well as recruitment and retention of study participants, and monitoring and evaluation of these activities. The Training and Professional Development instrument asked about staff training and professional development, including associated policies and procedures, opportunities and modalities, and monitoring and evaluation.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and to stimulate the discussion of possible best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources, a component of NIH. It stems from the NIH's commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.

64
USING EHRs FOR CLINICAL RESEARCH DATA MANAGEMENT
Robert P. DiLaura and Anil Jain
Cleveland Clinic Foundation, Cleveland, Ohio, USA

Electronic Health Record (EHR) systems enable access to large volumes of data held in patient care medical records as well as provide other advanced features. Healthcare information systems have grown steadily to meet these requirements. Conversely data management needs for clinical research have been met mostly through sponsored trials or federally funded grants requiring such things as validated systems or tight contractual controls around who can see and “own” study data. It is easy to conceive of using EHRs, with all of the resources invested in building these patient care systems, to also be used to manage clinical research data. Such opportunities are being diligently explored around the world because of the dramatic potential benefits including immediate access to...
Electronic Linkage of Trial Participants: A Resource for Evaluation of Long-Term Safety and Ongoing Efficacy

Ian Ford and Heather Murray
University of Glasgow, Glasgow, UK

Most clinical trials are designed with a focus on efficacy. Many safety outcomes (eg cancer) have inadequate follow-up for detection of a safety signal. On completion of the trial there is uncertainty about whether any benefits observed within-trial will be sustained or enhanced with extended follow-up. Developments in electronic health records are ongoing worldwide. Electronic linkage of trial participants to databases of routinely collected health data provides a potential solution for long-term follow-up.

We describe our experiences in Scotland of electronic linkage to national databases of hospitalizations, cancers and deaths. Issues and pitfalls in extended follow-up will be reviewed and the potential illustrated using follow-up of the 6595 participants in the West of Scotland Coronary Prevention Study (WOSCOPS). WOSCOPS was the first major outcome study of a statin vs. placebo in subjects without a history of myocardial infarction (mean follow-up 4.9 years. At the time, many were concerned about the safety of cholesterol lowering. Despite positive results (31% reduction in CHD death or non-fatal MI, p < 0.001, 33% reduction in CV mortality, p = 0.033, 22% reduction in all-cause mortality, p = 0.051) a long-term follow-up was planned. The results of this low-cost computerized extended follow-up of almost 10 years demonstrated that non-CV and cancer mortality were well balanced between the two treatment groups. CV events continued to be reduced in the group originally randomized to a statin with a risk reduction approximately half that seen in the original trial despite the two treatment groups being balanced with respect to statin treatment after the study finished. Death or hospitalization due to CHD was reduced by 20% (95%CI (10%,29%)), p = 0.0004 in the 10 years after the study and by 25% over the full period providing evidence of long-term safety and significant on-going benefit from almost 5 years of treatment with a statin.

Implementation of a Neurological Protocol in an Epidemiological Study of Patients with Type 1 Diabetes (T1D)

Barbara Waberski, Patricia Cleary, Daniel Rosenberg, Kandy Klumpp and Cathy Martin
The George Washington University, Rockville, Maryland, USA

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive diabetes treatment, compared to conventional treatment, led to risk reductions in the onset and progression of early microvascular complications of T1D. Preliminary results from The Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study indicated that the benefits of intensive therapy on neuropathy persisted for eight years after DCCT closeout.

In the 13th year of follow-up, EDIC reimplemented a neurological protocol last completed by subjects at DCCT closeout in 1993. 1,327 (92%) participants are expected to complete the Autonomic Nervous System (ANS) Testing and Peripheral Nervous System Testing within two years. A quantitative sensory measure (Vibration Perception Threshold or VPT) test, a neuropathy quality of life questionnaire, and an autonomic symptom questionnaire were included.

Implementation of the neurological protocol involved steps to guarantee data collection and quality paralleled that of the DCCT. Certified neurologists and electromyographers from each site were certified to perform the neurological exam and nerve conduction studies. Study coordinators were centrally trained and certified to use ANS and VPT equipment. Eight Electronic Case Report Forms were designed as well as a new web-based central data management system (CDMS), allowing for edits at the point of data entry. To maintain the integrity of the data, high criteria QC measures have been put in place for assessing the value of testing and scoring of complex tests such as the ANS and VPT. Implementation of an advanced CDMS has also allowed for timely dissemination of results to physicians, nurses, and study participants. Results include the integration of DCCT and EDIC neurological outcomes based on complex and standardized algorithms.
P 02
A FLEXIBLE DATA MANAGEMENT SYSTEM FOR GENERAL CLINICAL RESEARCH
Shawn F. Harris
Constella Group, LLC, Durham, North Carolina, USA

Researchers at Constella Group, LLC, frequently face decisions regarding the use of commercial-off-the-shelf (COTS) study management systems versus building custom systems to support federally sponsored clinical studies. Considerations include mitigating the necessary complexities of systems designed to support FDA regulated research and optimizing the flexibility and adaptability required by ongoing and future studies.

One such customized system, designed and built using in-house expertise, needed to be web-based to support off-site users, and designed in such a way that it could be adapted to similar studies without a great deal of time and effort. The system that was developed was based on an SQL Server database and was mostly programmed using ASP.NET, with support from stand-alone Visual C# programs. Some unique features of the system include:

- A calendar component used to schedule home visits based on the availability of team members in the region.
- Computer Assisted Telephone Interviewing (CATI) and Computer Assisted Personal Interviewing (CAPI) systems.
- A “task-driven” design – new tasks are automatically assigned when the status of a previous task has changed, email reminders are generated when tasks are overdue or require attention, and sets of tasks may differ between the control group and the treatment group participants.

This poster illustrates the advantages of choosing an in-house tool over a commercially available one, and will describe the design and features of the custom application. Emphasis is placed on showing the features which easily carry forward from study to study, using examples from several studies. The unique attributes of these studies support the need for a high level of customization.

P 03
DEVELOPING A DATA AND STUDY MANAGEMENT INFRASTRUCTURE TO SUPPORT GENERAL CLINICAL RESEARCH
David A. Johndrow
Constella Group, LLC, Durham, North Carolina, USA

Whether you work for a CRO, an academic institution or a branch of the government, you have probably encountered the “general clinical research” dilemma. On the one hand, the research is so flexible and of such variation that it does not lend itself well to rigid standards (e.g. CDISC, database design, casebooks). On the other hand, not having good standards in place has resulted in lost efficiency through duplication and often leads to the existence of processes or systems that are error prone due to their “one-off” nature.

How can you standardize casebooks or databases when you have no idea what studies will be in place a year from now? The truth is, while you might not be able to standardize to the same level you might within a series of clinical trials, you can benefit greatly from developing a standardized infrastructure that defines the people, processes and technology necessary to guide your organization to making the right choices, consistently.

This presentation will discuss some of the challenges encountered by Constella Group, LLC when confronting studies with great variance, and how an infrastructure toolkit has enabled us to diversify and speed up our ability to setup and conduct studies. For example, by going through a process that weighs study attributes such as size, need for speed, regulatory requirements, reporting requirements, data acquisition points, etc., we can select the appropriate data collection tools. Employing the toolkit, we ensure the right tool is selected for the job. The presentation will demonstrate features of the infrastructure toolkit and the benefits gained from developing this approach.

P 04
MANAGING DATA COLLECTION AND STORAGE IN THE WOMEN’S HEALTH INITIATIVE EXTENSION STUDY
Gretchen Van Lom, Mike Tennyson, Doris Nodtvedt and Bernadine Lund
Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

The Women’s Health Initiative Extension Study (WHI-ES) is a follow-up study to the Women’s Health Initiative, a large multi-center longitudinal study of postmenopausal women conducted 1993–2005. The WHI-ES involves health-tracking of participants without intervention through 2010. The data management system includes a centralized, high-volume scanning operation, Oracle database servers, and a secure web-based application which provides 39 Field Centers nationwide access to the central database for data entry and reporting. As of August, 2006, over 115,000 women had consented to the WHI-ES. Each participant receives an annual mailing from the WHI-ES Clinical Coordinating Center (CCC) containing two to four Optical Mark Recognition (OMR or “mark-sense”) forms. The specific forms a participant receives depends upon the WHI study arm into which she was originally randomized as well as the number of years she has been in the WHI-ES. As completed forms are returned by participants to the CCC, they are scanned into the WHI Extension database (WHIX) using Pearson Opscan inSIGHT™ image scanners. As each form passes through the scanner, the system loads and validates the
responses into WHIX while simultaneously capturing an image of the form. Both the data and images from scanned forms are immediately available in electronic format to the Field Centers via the web application. The paper copies of the forms are later destroyed. The scanning system is a highly efficient, accurate and low-cost data entry solution. During the 12 months from November, 2005 through October, 2006, the CCC scanned a total of 329,550 participant forms (508,837 individual sheets) using the equivalent of a single staff member.

P 05
FOLLOW-UP OF PARTICIPANTS IN THE WOMEN’S HEALTH INITIATIVE EXTENSION STUDY
Julie R. Hunt, Gretchen Van Lom, Jill Shupe, Doris Nodtvedt and Bernedine Lund
Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

The Women’s Health Initiative Extension Study (WHI-ES) is a follow-up to the Women’s Health Initiative, a longitudinal, nationwide study of postmenopausal women enrolled into either the Clinical Trial (N = 68,132) or Observational Study (N = 93,676). The CT consisted of three interventions: low-fat eating, hormone therapy, and calcium/vitamin D supplementation. Participation in the CT interventions began in 1993 and ended in 2005. At that time, willing women joined the WHI Extension Study for an additional five years of follow-up without intervention (N = 115,332). To collect follow-up data, the Clinical Coordinating Center (CCC) mails up to three packets annually. All packets contain a cover letter, health form(s), postage-paid return envelope, and pencil. All participants receive a health update form; those originally enrolled in the hormone trial also receive questions on hormone use. Each year, a packet is mailed two months prior to the participant’s enrollment anniversary. Completed forms are returned to the CCC for scanning. Three months after the first mailing, non-respondents are mailed a second packet; a third packet is sent to non-respondents two months later. Clinic staff contact women by telephone who: did not respond to the mailings; do not have a deliverable mailing address; are unwilling/unable to complete forms by mail. Throughout the process, the WHI database is updated with address corrections provided by USPS; clinic staff search for those with no forwarding information. Participants are also mailed a WHI newsletter annually, to provide study updates and help maintain correct addresses. By the end of the first year, 98.1% of WHI-ES participants had completed a health update (84.8% responded to the first mailing, 7.9% to the second/third mailing, and 5.4% to telephone follow-up).

P 06
AN ELECTRONIC TRANSFER PROCESS FOR OCT IMAGES
John W. Lum, Roy W. Beck and Brian Becker
Jaeb Center for Health Research, Tampa, Florida, USA

The Diabetic Retinopathy Clinical Research Network (DRCRnet) is a collaborative network dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema and associated conditions. Coordinated by the Jaeb Center for Health Research, DRCRnet conducts multiple concurrent studies at more than 175 sites in the US and Canada. A clinical procedure that is used in many DRCRnet protocols is Optical Coherence Tomography (OCT), a noninvasive method for measuring the thickness of the central retina. It has become a standard tool in the management of patients with diabetic macular edema (DME). OCT is a diagnostic imaging technique, which uses low-coherence interferometry to produce cross-sectional tomograms of the posterior segment eye structures. In DRCRnet studies, the OCT images from patient exams are transferred to a reading center for assessment and the grading result then entered into the coordinating center’s study database. Until recently sites performed this transfer by manually saving the image files to diskettes and shipping to the reading center with paper transmittal forms for processing. We have now developed an internet-based electronic transfer application for the complete process of image acquisition, transmittal, assessment, and entry of grading results into the central database. We will present the application algorithm, discuss technical and procedural issues that were encountered during the process, and review data and personnel related benefits to study conduct.

P 07
A REUSABLE TEMPLATE SYSTEM FOR FASTER WEB CRF DEVELOPMENT
Pamela S. Moke, Roy W. Beck, Lee Anne Lester and Mitchell Dupre
Jaeb Center for Health Research, Tampa, Florida, USA

The Jaeb Center coordinates several large research networks including the Diabetic Retinopathy Clinical Research Network (DRCRnet), Diabetes Research in Children Network (DirecNet), and the Pediatric Eye Disease Investigator Group (PEDIG). Within these networks, multiple protocols are in concurrent development by investigator based committees collaborating with the Jaeb Center. As protocols are approved, a study start date is set and the specifications released to the development group for implementation. As the number of protocols increased, we needed a method to maintain production levels while retaining the same highly customized CRF layout that our clinical investigators expect. An evaluation of existing development identified CRF forms and sections that are
primarily consistent across various protocols within each network. We then designed a reusable templating system (RTS) that consists of generic CRFs for common data collections (Baseline History, Pre-Existing Conditions, etc.), modifiable attributes for protocol-specific messages, the ability to show or hide specific fields or sections, and similar flexibility to meet protocol requirements. RTS has been completed for DRCRnet and DirecNet and is in development for PEDIG.

We will present the underlying logic and infrastructure for the RTS approach and show examples of CRF templates. We will also discuss the impact of RTS on development time, personnel resources, and quality assurance procedures.

P 08
DATA SHARING BY ACUTE STROKE CLINICAL TRIALS
Selma C. Kunitz and Stacie Trollinger
KAI Research, Inc., Rockville, Maryland, USA

To improve the use of acute stroke interventions, the National Institute of Neurological Disorders and Stroke, NIH funded a series of independent grants called the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS). SPOTRIAS stroke center investigators have evolved into a cross-country Network that collaborate on early phase clinical trials, share data, and train new investigators. Importantly, the SPOTRIAS Network centers are now aggregating data from their systems. KAI Research, Inc. (KAI) has worked with the data/statistics teams of the Network centers to provide the data management infrastructure. KAI and the data/statistics teams ensure that the definitions, structures, and export processes facilitate data aggregation for meta-analyses. In less than two years the SPOTRIAS Network has aggregated data from six stroke centers and created the SPOTRIAS Common Clinical Database (CCD). KAI maintains the SPOTRIAS CCD which contains information on more than 5,500 stroke cases. The keys to making the data aggregation possible follow:

1. Researchers and data managers collaborated to lay ground work for CCD – The Principal Investigators identified and defined the data elements they would collect across studies. KAI and the data/statistics teams made the necessary technical revisions to those data elements to build a data dictionary.
2. Conversion of data into Extensible Markup Language (XML) – Each SPOTRIAS Center extracts data from its unique data system and converts it into XML. The XML files are submitted to KAI using secure file transfer protocol (ftp) and KAI uploads the XML files into the CCD, a SQL server database.

Now that the SPOTRIAS Network has established its data sharing processes, it is focusing on improving the quality of the clinical data. KAI and the data/statistics teams are working to develop and improve the quality review processes.

P 09
TRAINING CLINICAL AND DATA MANAGEMENT STAFF IN PROTOCOL IMPLEMENTATION
Reesa L. Laws and Pierre LaChance
Kaiser Permanente Center for Health Research, Portland, Oregon, USA

Adequate training in protocol implementation, data collection, and data management are vital to a multi-site clinical trial’s success. As the Data Coordinating Center for several multi-site clinical trials, we have developed an effective methodology for training clinical site staff. Our training focuses on Good Clinical Practices, forms administration, data management, and our secure, web-based data system. We conduct an annual recertification process with site staff to ensure continued adherence to the protocol throughout the life of the project. We also create and review trial monitoring reports focusing on site compliance, data accuracy, and timeliness. These early reports help us identify potential inconsistencies in procedures or lack training, which allows us to quickly remedy any identified problems. These reports are supplemented with site visits, which offer another opportunity to determine if additional training is needed.

P 10
IMPACT OF CHANGING FROM PAPER BASED DATA COLLECTION TO ELECTRONIC DATA CAPTURE ON THE ACTIVITIES OF THE COORDINATING CENTRE OF THE NCIC CTG
Beverly Koski, Tracey Messerschmidt, Lam Pho, Anna Sadura, Dora Voskoglou-Nomikos, Jean Powers and Belinda Vandersluis,
National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) conducts national and international multicentre Phase I, II and III clinical trials in symptom control, cancer prevention and treatment. The Group has upwards of 75 Canadian member sites and 60–70 studies active within a given year and collaborates with the CTSU, other cooperative groups and international sites. Historically the NCIC CTG has used a paper case report
form method of data collection combined with coordinating centre review. The planned change to electronic data capture (EDC) has a direct impact on all levels of activities related to the development, conduct, monitoring, auditing and reporting of the clinical trials.

The experience and framework in place for the paper based system facilitated the identification of the processes and documents that required change. The most significant impacts on the coordinating centre were with regard to: the need to understand and relate the documentation and terms provided by the supplier of the EDC system to the language and structure of the NCIC CTG; the level of precision allowed/required in defining site and coordinating centre permissions and actions because of the need to program these directly into EDC (e.g. user and site administration, data entry, review and reporting); the integration of the data from the EDC system with existing legacy systems (e.g. roster, ethics approval, registration); changes to SOPs and work instructions; education/training for the sites and the coordinating centre.

The poster will describe the key processes that were affected and changed, what they were changed to and the overall impact on how the activities of the coordinating centre were organized.

P 11
PLANNING THE CHANGE FROM PAPER BASED TO ELECTRONIC DATA CAPTURE
Beverly Koski, Qianru Wu, Lam Pho, Anna Sadura, Dora Voskoglou-Nomikos and Jean Powers
National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) conducts national and international multicentre cancer Phase I, II and III clinical trials in symptom control, cancer prevention and treatment. Approximately 8000 paper CRFs are received for trials in 10 different disease sites monthly. The scope of the NCIC CTG trials is broad and the data collection requirements continually evolve in order to accommodate different trial designs and treatments.

The essential change from paper based to electronic data capture provided an opportunity for clinical and database teams to collaborate in the planning of the implementation of electronic data capture (EDC) for new studies. The plan needed to take into account: the characteristics of the EDC system; how the eCRFs and data dictionaries for the new trials developed in EDC should be defined in order to facilitate consistency and efficiency in the development of subsequent trials within the system; how to accommodate current coordinating centre differences in data collection requirements and database design between Phase I/II and Phase III trials; and how documentation should be created and managed.

The key characteristics of the EDC system, the planned steps and types of personnel involved in the implementation, the templates/lists of the resources/dictionaries for developing new trials, and the maintenance and updating of these resources will be described.

P 12
A PAPERLESS, DISTRIBUTED DATA MANAGEMENT SYSTEM FOR MULTI-CENTER CLINICAL TRIALS
Uma Ramamurthy, Xingquan Lu, Zhou Ji, Prasanna Velamuru, Swapna Bavanaka, Kiran Rajaya, Larry E. Kun and James M. Boyett
Pediatric Brain Tumor Consortium, Memphis, Tennessee, USA

We present a paperless, distributed data management system designed and implemented in the multi-center Pediatric Brain Tumor Consortium (PBTC). The Consortium implemented a paperless data management system starting with its first clinical trial in 1999. All data communication between clinical sites and the Operations and Biostatistics Center (OBC) in Memphis, TN occur via Virtual Private Network (VPN) connections. Patient registration is an online, web-based system. Ten clinical sites collect data using laptops and upload the patient database to OBC to generate the central database, PedBraTum. With PedBraTum, we have set-up automated, online data reports for investigators. Automated systems monitor the PedBraTum database for delinquent data on a daily and weekly basis, and send email reminders to sites to ensure timely data collection.

Auxiliary databases in OBC provide for regulatory data, administrative data, invoice data for patient/research costs, and data from correlative studies namely pharmacokinetics, biology, neuro-pathology and neuro-imaging. The auxiliary databases link with the PedBraTum database to provide a comprehensive system for paperless data management in this clinical trials setting. Regulatory and consent documents are faxed from clinical sites to the fax-server in OBC that receives the faxed papers as electronic documents on our network. These electronic faxes are hyperlinked within our databases to enable easy access for the OBC staff. We designed and implemented, in 2001, the first all-electronic neuro-imaging studies' transport and archival system for the PBTC Neuro Imaging Center at Boston.

This paperless, distributed data management system has successfully facilitated 22 clinical trials to-date, ensuring timely data collection for 748 patients, HIPAA compliance for data security and patient confidentiality.
Every time a dataset is created, whether for data management purposes or for statistical analyses, it is imperative that each variable be reviewed. Not only should the evaluation provide summary statistics and graphical displays to detect data errors, it should also present the results in a thorough, yet succinct manner. To accomplish this goal, descriptive summaries for each variable should be created according to their characteristics. As simple as this task sounds, no major commercial statistical software package has a shell procedure to do it.

The best available option for generating descriptive data set summaries is found in the Hmisc (Harrell Miscellaneous) package for the R statistical programming environment. However, these freely available tools have two main drawbacks. First, they require the user to invest a substantial amount of time in learning a new programming language. Second, most statistical and clinical coordinating center datasets are stored as SAS files which are not straightforward analyzable using R.

The following presentation introduces a SAS macro that automatically creates a thorough and succinct data book where the variable type (dichotomous, ordinal, nominal, continuous, etc) dictates which summary statistics are displayed. The SAS macro combines Hmisc functions, Sweave, and LaTeX to create an innovative data book. All the processes are run behind the scenes; as such anyone with access to SAS can create these displays with no need to learn a new programming language.

The Ottawa Statement is a consensus document that aims to guide the implementation of global trial registration. Endorsed by individuals and organisations throughout the international research community, the Statement recognises that public availability of information about all trials in healthcare is essential to ensuring ethical and scientific integrity in medical research. In 2004, the Canadian Institutes of Health Research hosted an open meeting in Ottawa, Canada, and invited interested parties to contribute to a policy on trial registration. The assembled group - consisting of interested investigators, consumers, journal editors, policymakers, and industry representatives - discussed a set of guiding principles. These principles, published as the Ottawa Statement Part I, propose that every initiated trial be associated with a unique identification number and publicly register a standardized “minimum dataset” of protocol items. Protocol amendments are added as needed.

In 2005–2006, the Statement was further refined in three open meetings and Part II was added. Part II focuses on implementation and results reporting, including disclosure of both harms and benefits identified in the trial. Challenging areas for the implementation strategy remain, in particular recommendations for the maximum length of time from trial completion after which investigators are expected to disclose their results on the register; the format of results reporting; and whether interpretation of results should be included on the register.

Contributions and signatories to the Ottawa statement are invited (http://ottawagroup.ohri.ca/index.html).

Since 2000 in Italy is operative the National register on clinical Trials (Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali. Up to now it contains more than 3500 clinical trials in all different research fields and it is managed by National Medicines Agency. More than 600 clinical studies has been performed every year and in 2005 the distribution for phase I is the following:

- Fase I 2,3%; Fase II 36,0%; Fase III 49,5%; Fase IV 10,7%; Bioeq/bioav 1,5%

Pharmaceutical companies are sponsor in more than 73% of all clinical trials but there is an important 27% of independent research. (universities, non-profit organization, scientific association etc.). Many reports have been published during these years and all of them are available at the Osservatorio Web-site (http://oss-sper-clin.agenziafarmaco.it). Since 1 December 2005 the information are also available for public consultation. A specific
A questionnaire is developing for citizens in order to know their satisfaction grade on this matter and the results will be presented. An open discussion forum has been developed in order to collect all the suggestions from sponsors (profit and non-profit) and the major comment, made for optimized the entire system will be presented.

**P 16**

MANAGING LARGE SCALE CLINICAL TRIALS THAT UTILIZE CONTROLLED SUBSTANCES

Mary Kay Cormier, Dennis Raisch, Dean Argyres, Michael Chavez, Frank Lueddeke, John Recio and Melissa VanKaden

Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC), Albuquerque, New Mexico, USA

The VA Cooperative Studies Program CRPCC has coordinated numerous large scale, multi-site, clinical trials involving controlled substances—both narcotic and non-narcotic. Controlled substance pharmaceuticals are closely regulated by the United States Drug Enforcement Agency (DEA), and must meet stricter Federal regulations than just the standard United States Food and Drug Administration’s (FDA) Current Good Manufacturing Practices (cGMP) requirements. As a result, controlled substance clinical trials present unique problems and challenges for the project team.

The purpose of this presentation is to describe the use of proven project management techniques used during the design and conduct of controlled substance clinical trials, and to illustrate how these techniques can enable complete drug accountability and compliance within a strictly regulated environment. The highlighted aspects will include management of DEA registrations and reporting systems, licensing issues, and purchasing requirements. Additionally, this presentation will cover the design and management of study specific packaging, drug shipping and receiving, inventory control requirements and product reconciliation at study termination. Specific areas to be covered include information technologies, clinical materials management, biopharmaceutics and pharmacokinetics, quality management and project management.

The end goal of the presentation is to provide a useful model of proven and effective project management techniques and processes to ensure complete drug accountability and compliance, which can be used in future multi-site clinical trials utilizing controlled substance pharmaceuticals.

**P 17**

K-MEANS CLUSTERING IN CLINICAL DATABASES USING SQL

Ellis Clarke, Lea Liu and Bruce Barton

Maryland Medical Research Institute, Inc.

Baltimore, Maryland, USA

We introduce an implementation in SQL of the K-Means clustering algorithm. This is useful for direct data mining of clinical databases and eliminates the need to export the data to a statistical package for analysis. Errors in exporting the data and in variable selection for export are eliminated and there is no need to repeatedly create new export files for revised or updated data. Also, the clustering analysis does not need to be done by a statistical programmer using a separate proprietary software package. The implementation’s efficiency is increased with native relational database methods, such as table indexing. Data from the NHLBI Growth and Health Study (NGHS) are used for demonstration, with several combinations of the number of variables and of clusters. The preprocessing and normalization of the data is also done in SQL. Clustering results from the SQL implementation are compared with results from a SAS clustering procedure, using the same data.

**P 18**

IMPACT OF THE HUMAN TISSUE ACT 2004 ON ACADEMIC CLINICAL TRIALS: METHODOLOGY OF A PHASE II TRIAL (TRAPEZE) INVOLVING THE COLLECTION OF HUMAN TISSUE

Darren Barton, Emilio Porfiri, Nicholas James and Jennifer Barnwell

University of Birmingham, Birmingham, United Kingdom

The Human Tissue Act (HT Act) 2004 emerged following extensive review of the law relating to retention of human tissue and use of human tissue. This Act affects organisations that are involved in removal, storage, use and disposal of human tissue throughout England, Wales and Northern Ireland. The impact of the HT Act on clinical trials relates to additional financial, organisational, methodological and technical aspects of tissue collection sub-studies. These need to be addressed in order to comply with current legislation. Financial aspects of the Act relate to additional equipment e.g. labeling systems, additional security and staff costs. Trapeze is a UK based Phase II study which is currently in the recruitment phase and opened in 2004. Tissue collection aspects relate to collection of blood serum and formalin fixed tissue blocks. Standard Operating Procedures (SOP) have been developed to comply with the HT Act and the Human Tissue Authority: Code of Practice. Every blood sample collected is assigned a unique identifier which is located on pre-printed aliquot labels. Each label contains the following information: unique identifier, date of sample, patient date of birth and
study name. The use of pre-printed freezer-safe labels prevents any translation mistakes when free-hand labeling. A sample transfer form is used to record the patient trial ID and details recorded on the sample label. The sample details are recorded on a central database upon arrival at the coordinating centre. The collection of tissue blocks will follow a similar SOP. It is the patient consent procedures and robust labeling, storage and individual sample tracking, which form the essence of the HT Act. It is important to consider these issues when planning & financing new or reviewing ongoing clinical studies.

P 19
FROM ELECTRONIC DATA CAPTURE TO CLINICAL DATA WAREHOUSE:
THE ITALIAN ASSOCIATION FOR PEDIATRIC ONCOLOGY (AIEOP) CLINICAL TRIAL SYSTEM
Federica Ronchetti1, Luca Dematte1, Gregorio Greco1, Andrea Pession2 and Marisa De Rosa1
1CINECA Inter-University Consortium, Bologna, Italy
2University of Bologna, Bologna, Italy

The Italian association for pediatric onco-ematology, AIEOP, was a pioneer in the use of internet based clinical trials for all their studies, starting twenty years ago in collaboration with CINECA university consortium, the largest Italian supercomputing center. This allowed the group to develop a very sophisticated and complete structure starting from the electronic data capture, complete with an integrated e-query system, up to a Clinical Data Warehouse integrating patients data, study information, diagnostic images, lab and genetic data, protocol data, in only one central database. The investigator, the statistician, the data manager, the protocol coordinator, the pathologist and the surgeon can access the CDW according to their user profiles.

Currently, the AIEOP system contains two patient registries, seven disease-oriented registries and 63 clinical trials (1 on start-up, 12 open to accrual, 11 on-going, 39 closed). 29288 patients have been registered in the central database by 90 centers. The advantage of using a clinical data warehouse is to have an integrated environment that allows the re-use of the pathology database and the electronic CRFs, to have standard codes for every study and to be able to do multi-dimensional analysis across trials.

P 20
USING WIKI FOR IT SYSTEM DOCUMENTATION
Brian Becker, Pamela S. Moke and Roy W. Beck
Jaeb Center for Health Research
Tampa, Florida, USA

The Jaeb Center for Health Research is the coordinating center for several large collaborative research networks conducting clinical studies at more than 450 sites in the US and Canada. All study protocols use real-time data collection with web-based case report forms. Supporting this effort is an infrastructure of company servers, web servers, databases, firewall, and similar components, all of which have configuration, maintenance, and security specifications.

Keeping the documentation for this infrastructure updated and organized is a critical component of the company’s quality assurance standards. To be efficient and effective, just having the documentation isn’t enough; the content must be organized, up-to-date, manageable, and readily accessible to users. To address these issues in our IT department we have implemented a collaborative authoring web-based application known as a Wiki. Wiki provides a cross-linked, hierarchical category-based system that allows documentation to be linked across multiple topics. For users, this provides quick cross-topic access to relevant documentation based on their individual needs. The Wiki also provides users with a powerful search engine to identify documentation on a given subject. For authors, the Wiki provides automatic version control, version comparison, and a role based authentication scheme, all of which allow multiple stakeholders to contribute to system documentation while an administrator maintains overall control of the information.

Prior to implementing the Wiki, we used static word processing documents organized in file folders. The Wiki transition was not an easy one but the result is a successful system for documentation organization and tracking. We will present lessons learned from this project and discuss some of the innovative options that are available within the Wiki environment.

P 21
DEVELOPMENT OF STATISTICAL METHODOLOGY ACCOMODATING INHERENT OUTLIERS TO NORMALIZE REPORTING OF REAL-TIME DATA FOR PERFORMANCE-IMPROVEMENT PROJECTS
Sharon R. Kimmel, Valerie Rupp, Gary Haas and Marna Greenberg
Lehigh Valley Hospital & Health Network, Allentown, Pennsylvania, USA

Hospitals are increasingly using business query-applications for real-time descriptive statistics tracking and reporting. Unusual cases, inherent in healthcare processes, may skew reported descriptives. We used McKesson’s
Horizon Business Insight (HBI) to evaluate Emergency Department (ED) performance of patients presenting with acute coronary symptoms and evaluate outcomes of an improvement initiative. Time-to-diagnoses and time-to-treatment modalities were captured. To ensure correct data, random chart audit was performed. Outcome measures report mean rather than median statistics. Analyses (N = 888) of 14-month raw data reported standard-deviations beyond mean values and +skew ratios >2.5 suggesting extreme outliers most likely representing unusual, albeit clinically justifiable times. Real-time chart review of outliers defeated purpose of immediate reporting. Door-to-ED-Discharge (DED) and Door-to-first-positive-troponin (DFPT) variables were explored to develop the most plausible statistical stabilizing method (SSM) for imputing ceiling scores into HBI algorithms without compromising reporting “normal” mean times. Z-score, Winsorizing, 80/20 cropping, and gap-identification methods were applied across baseline and three post-intervention quarters. To identify intervention affect times were compared using ANOVA, Bonferroni post-hoc. Excluding z-scores ranges were: DED: mean 111.50–157.97, median 112.50–123.50, skew-ratio −4.86–69.21, kurtosis-ratio 0.74–318.42. DFPT: mean 269.98–363.16, median 268.50–302.50, skew-ratio −0.56–31.49, kurtosis-ratio −3.28–58.12. DFPT was anticipated to vary across time-frames in response to the intervention. DED was anticipated to stay same. ANOVA results reported varying statistically significant difference (SSD) across SSM. There were no SSD in DED across all methods. 80% cropping was the SSM to most likely reduce skew and least likely to discern SSD. Discussion will include HBI demonstration, comparison of central tendency measures, HBI and clinical significance of SSM, outlier chart review and inferential comparison findings.

P 22
RULE BASED AUTOMATED SUBJECT TRACKING FOR CLINICAL TRIAL DESIGN, MANAGEMENT AND REPORTING
Wenle Zhao and Yuko Palesch
Medical University of South Carolina
Charleston, South Carolina, USA

The CONSORT statement [ref: JAMA, April 18, 2001—Vol 285, No. 15] requires that the subject consolidation standards must be followed in randomized clinical trial reporting. The study sample groups for the reports need to be identified based on rules pre-specified in the statistical analysis plan and on the information collected during the study. To achieve this goal, a rule-based automated subject tracking module is developed within a web-based clinical trial management system by the Data Coordination Unit at the Medical University of South Carolina. In the protocol design stage, the study is divided into phases (e.g., baseline, treatment, and follow-up) and visits starting from enrollment. Study progress report, and schedule of payment to the clinical sites can be linked to each study phase and visit. Logic conditions enabling subjects to be moved from one study phase to the next are specified with SQL statements, and evaluated with study data collected. In addition, subject groups used in the trial reporting and data analyses are defined based on the study statistical analysis plan and the study database. During the study period, when a subject leaves one study phase, the subsequent study phases will be determined automatically based on the collected data. This design ensures the objective accountability of all study phases and subjects. It also enforces site personnel to follow the study protocol. Study progress data can be directly reported from this system. The path from enrollment to current phase will follow the protocol. Each trial report will link to one specific study sample (e.g., intent-to-treat or per protocol). The sample membership is automatically identified by the subject tracking system, based on the clinical data.

P 23
THE SOUTHWEST ONCOLOGY GROUP STUDY COORDINATOR EVALUATION APPLICATION
Angela Smith
Southwest Oncology Group, Seattle, Washington, USA

The Southwest Oncology Group (SWOG) is a large multi-site Cooperative Group responsible for the data collection and analysis for hundreds of clinical trials. Since 2002, SWOG has gradually transitioned from a paper-based data collection system to one that is now primarily online. Among its benefits, online data submission allows for the electronic storage of patient research records, which has changed the way those data can be processed. Each SWOG-coordinated study has a designated study coordinator who oversees the study conduct. The study coordinator is typically a physician within the Group whose responsibilities include review of all patient data received, and approval of the eligibility, treatment, and response coding performed by central data coordinators. Until July 2006, this review process had been paper-based, requiring data received by the central office to be copied and forwarded to the study coordinator, and evaluation forms to be printed and mailed when necessary. Study coordinators were required to maintain these research records at their clinic, and to complete their review on the paper forms which were then mailed back to the central office.

The Study Coordinator Evaluation Application replaces this paper-based review process with a web-based application that allows the Study Coordinator real-time access to all data received for their study patients. In addition, the application makes it clear which patients need evaluation, and allows for those evaluation forms to be completed online. The Study Coordinator Evaluation application has been very well-received as a welcome increase in efficiency for the review of patient data.
RESEARCH UNITS WITHIN LARGE INSTITUTIONS SHOULD MAINTAIN THEIR OWN SECURITY PORTAL AND SINGLE POINT OF TRUTH (SPOT) DATABASE

Gladys McPherson, Allan Walker, Alison McDonald and John Norrie
University of Aberdeen, Aberdeen, UK

Trials Units are often contained within large institutions. The management of multi-centre trials by such Units necessarily involves collaborators from external institutions. Traditionally, institutional IT departments have been wary of providing user accounts to external research collaborators. User accounts imply membership of the institution and acceptance of a set of user terms and conditions with additional risk exposure and administration overheads. This can result in Units taking on the tasks of user-maintenance and authentication, often in an ad-hoc, per-trial manner. As Units get involved in managing further trials over time this model is not sustainable. Provision of Unit-wide reporting facilities consumes more resources than expected; individual research collaborators become involved in different trials and the administration overhead falls upon the Unit; software interfaces have no cross-trial memory, jeopardising the success of project web-interfaces.

A SPOT database goes a long-way to resolving these issues. It provides a single sign-on for collaborators, affording external and internal collaborators the same status. It aggregates information about people, associates rights with each person and feeds that information to all applications, reducing the administration overhead involved with maintaining collaborator details and a Unit-wide reporting mechanism.

A SPOT database has two other advantages. The security portal developed on the back of this database can become the keystone for more sophisticated trial-management systems. Additionally, such a database can easily be integrated into institution-wide systems, giving institutional IT departments the opportunity to make resources available to trial collaborators without incurring seemingly unacceptable costs. This presentation will outline the pros and cons of a SPOT database and describe our experience in its implementation.

ELECTRONIC DATA COLLECTION SYSTEMS: IT ALERTS

Gladys C. McPherson, Alison McDonald and John Norrie
University of Aberdeen, Aberdeen, UK

In today’s environment of increasing utilisation of electronic data collection it is possible for automatic alert systems to contribute in several ways. These systems can aid the research nurse, the clinician involved in care of the patient or the study centre staff. Some examples of alerts are:

- Immediate reporting of data values which exceed some cut-off value and therefore require some action to be taken. In one of our recent RCTs of intensive care post-discharge review clinics if a Hospital Anxiety and Depression Scale (HADS) is below a certain threshold value the patient is automatically referred to a psychologist. An email is sent to the research nurse and the appropriate psychologist and the relevant questionnaire attached for reference.
- Research nurses can be alerted that clinic visits are due
- Participants are to be telephoned for questionnaire completion
- They should write to a GP to ensure the status of the patient before contact (this is currently being used in two studies from our Group involving patients who have been in intensive care or high dependency units)
- Study websites may alert research staff of missing or anomalous data
- Study websites may alert the central study office when recruitment is slow

Alerting systems may run directly from the study database e.g. in response to update triggers on the tables, or from a stored procedure run as a job on the database server either once or several times a day. Alternatively they may be run on the update of the Web page where an attachment file can be created in the appropriate format (e.g. an Adobe PDF file which can be read with free software).

EVALUATING A DEVELOPMENT PLATFORM FOR WEB-BASED CLINICAL STUDIES

Pamela S. Moke, Roy W. Beck, Lee Anne Lester and Mitchell Dupre
Jaeb Center for Health Research, Tampa, Florida, USA

The Jaeb Center for Health Research has developed web-based clinical studies for more than six years using a proprietary development system. Our website has grown from a single study with 49 sites that performed only randomization to 20 concurrent studies at more than 450 clinical sites using real-time data collection, drug assignment, outcome evaluation, digital data transfer, and similar critical study tasks. While our original development system served us well, in recent years technological advances and changes in company needs have caused that core system to become outdated. We proposed a transition to a more current technology and, since this change would significantly impact all active studies as well as studies being developed for the coming year, we
undertook a detailed evaluation of company needs and available technology to identify the approach that would best fit our goals. We will discuss our reasons for replacing the environment including enhanced performance for users, shortened development time, and workforce availability and training. Factors applied to each potential development language (ColdFusion, .NET, PHP, Java) will be presented including in-house expertise and/or training requirements, future viability, security, cost, ease of transition from current language, length of transition time from old system, and built-in development tools. Finally, we will discuss our decision and key steps in the transition process.

As web-based electronic data collection becomes increasingly standard in clinical studies, the need to evaluate and update systems for current technology becomes a serious concern. The process we pursued to accomplish this goal for the Jaeb Center can be applied by other institutions addressing the same issue.

P 27
CONTROLLED TRIALS IN RARE DISEASES: HOW MANY? HOW INFORMATIVE? ADEQUATE?
Annalisa Perna1, Giovanni Antonio Giuliano1, Arrigo Schieppati1,2, Marco Costantini1, Mariya Ganeva1, Erica Daina1, Rumen Stevanov1 and Giuseppe Remuzzi1,2
1Mario Negri Institute for Pharmacological Research, Bergamo, Italy
2Nephrology and Dialysis Unit, Ospedali Riuniti di Bergamo, Bergamo, Italy

We conducted a descriptive survey in 71 rare diseases with MESH term selected from a list of 1608 orphan indications in order to evaluate the main characteristics and quality of randomized controlled trials (RCTs) in this neglected area. Through PubMed (1994–2005) we found 23459 titles, retrieving 351 abstracts of RCTs, from which we selected 168 full-published articles with parallel group design. The median number [interquartile range] of patients per study was 42 [26 to 76]. Sample size was calculated in 54 (32.1%) studies and stopping rules provided in 22 (13.1%). Adequacy of allocation concealment was the only quality descriptor, which improved from 1994 to 2005. Forty-five percent of the studies reported no differences between treatment interventions. ‘Negative’ trials recruited more patients, had a longer follow up and quality descriptors comparable or even better than those reporting ‘positive’ results. Trials showing a difference in favor of new interventions were published in journals with higher impact factor. The methodological quality of studies with industry sponsorship was comparable to those without. Blinding of participants and investigators was more frequently reported in presence of an industry support. In industry funded trials the follow up was halved as compared to non industry-supported studies: 6 vs 12 months respectively. We observed several deficiencies in reporting the trial design, which do not seem peculiar of rare diseases, but common to trials in other areas of medicine. However, omissions of important methodological details are particularly detrimental in rare diseases, where reliable data are so scanty and hardly reproducible.

P 28
ASSESSMENT OF TREATMENT EFFECT IN A MULTI-COUNTRY PHASE III CLINICAL TRIAL
David Huang
Wyeth Research, Cambridge Massachusetts, USA

Several statistical methods for evaluating treatment by center interaction from a multi-country study were explored. In brief, fixed effect, mixed effect and GEE method were considered. Fixed effect model is appropriate when the source of the variability is from patient sampling and within-center only while mixed effect model should be used when the between-center variability is notable. GEE method is for evaluating the overall treatment effect adjusting for the correlations between subjects within the same center. Response (outcome) data used in the analysis may be of individual patient or grouped data from a center. When the grouped data such as success rate are used (meta-analysis), issues may arise when the number of centers is large and the number of patients in each center is relatively small. GEE method and mixed effect model approach using the individual patient data are more robust in estimating the treatment effect across centers. Furthermore, mixed effect model using individual patients data is useful in estimating the inter-actions between treatment and center. A multi-country phase III clinical trial data analysis will be used to demonstrate the treatment was beneficial and consistent across all centers based on the appropriate statistical methods.

P 29
LESSONS LEARNED IN THE DESIGN OF AN EARLY PHASE CANCER CHEMOPREVENTION TRIAL
Krystal Sexton, P. H. Brown, R. M. Elledge, H. L. Weiss and S. G. Hilsenbeck
Baylor College of Medicine, Houston, Texas, USA

Background Early phase chemoprevention clinical trials play an important role in discovering effective ways to prevent cancer. The success of these trials depends on good estimates of variability and withdrawal rates, and these are often obtained from conventional therapeutic trials. However, the estimates from treatment studies may not be appropriate for prevention trials.
**Methods** A review of the literature showed that few early phase chemoprevention studies described the assumptions made in the sample size calculations. Here we report our experience with our breast cancer chemoprevention trial. Sample size calculations used data from our study of premalignant breast disease, assuming that up to 12% of subjects would fail to have pre- and post-treatment biopsies due to dropout or insufficient breast tissue.

**Results** The calculated sample size for this study was 50 subjects per arm. Eight-seven participants were enrolled, and 66 had paired biopsies. Of the paired samples, 52 (79%) were satisfactory, defined as presence of epithelial cells on H&E. This is modestly lower than originally anticipated. Altogether, 40% of the 87 participants either dropped or had an inadequate biopsy. If this had been anticipated in the planning stage, the target sample size would have been 62 subjects/arm. Alternatively, power to detect the expected effect size was reduced from 80% to 58%.

**Conclusions** Both dropout and inadequate biopsy rates were higher than originally assumed, affecting the power of the study. However, our enrollment and adequacy rates were consistent with the limited data available from other breast chemoprevention studies. The statistical assumptions made in the design of chemoprevention trials should not be conservative.

Supported by NIH grant U19-CA-86809.

P 30

**CAN WE IMPROVE RETENTION AND ADHERENCE IN PUERTO RICO FOR A U.S.-BASED LARGE CANCER PREVENTION TRIAL?**

Russell Campbell¹, Karen Anderson¹ and Elise Cook²

¹Cancer Research & Biostatics, SELECT, Seattle, Washington, USA
²UT M. D. Anderson Cancer Center, Houston, Texas, USA

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a randomized, double blind, placebo-controlled trial that examines whether selenium and vitamin E alone or in combination can decrease the incidence of prostate cancer. SELECT randomized over 35,500 randomized participants at approximately 420 sites in the U.S., Canada and Puerto Rico. The eight Puerto Rican sites randomized 1460 participants, 22% of whom are Hispanic Black. Problems were noticed early on with retention and adherence at the Puerto Rican sites. SELECT provided phone call and in-person mentoring to Puerto Rican sites. While sites did make improvements, as a whole the Puerto Rican sites still struggled. Since the semi-annual SELECT Workshops do not address Puerto Rican specific needs an intervention was needed to address their issues.

A day and a half workshop was held in Puerto Rico for all Puerto Rican SELECT sites that focused on the specific challenges unique to these sites. These challenges include the communication between site staff and participants who speak Spanish and English speaking SELECT representatives, the translation of study materials including consent forms, and newsletters into Puerto Rican Spanish, and the reluctance of Puerto Rican SELECT Principal Investigators and staff to provide written requests for funding or assistance from study leadership. This workshop provided a forum for SELECT staff in Puerto Rico to meet as a group, exchange ideas and receive intensive mentoring.

We will present the design and results of this culturally appropriate workshop as well as the responses of the attendees and the experiences of the SELECT Statistical Center’s staff in designing and conducting this workshop.

P 31

**PEDIATRIC RECRUITMENT FROM A COORDINATING CENTER’S APPROACH**

Rene Kozloff, Patti Shugarts and Laura Brown
KAI-Research, Inc., Rockville, Maryland, USA

The Best Pharmaceuticals for Children’s Act (2002) and the Pediatric Research Equity Act (2003) served as an incentive for an increase in pediatric clinical trials. The ethical and practical considerations of identifying, recruiting, and retaining children make the conduct of pediatric trials a challenge.

In a recent Harris Interactive Survey (2004), while 2/3 of US adults endorsed the need for pediatric research, only 25% would consider allowing their child to participate in a clinical study. In contrast, 59% of their children who have had the opportunity to participate in a trial, did. KAI, as the Coordinating Center for the Pediatric Pharmacology Research Units (PPRU) Network funded by the National Institute of Child Health and Human Development (NICHD), has developed an approach to successful recruitment in pediatric clinical trials.

KAI’s approach for recruiting children into clinical studies includes the development of a recruitment plan, strategies for recruitment during the pre-screening and screening phase, articulation of the role of the physician, study coordinator, and dedicated recruitment staff, and training of the physician and staff in enrollment. The recruitment plan and training sessions address and provide solutions for protocol design issues related to a pediatric population; issues related to racial, ethnic and socioeconomic differences in the target population; the challenges associated with participants of varying age and developmental level; and barriers to participation for the child and family. We will propose communication strategies for soliciting interest and incentives for participation in a research study.

The talk will address a “lessons learned” approach on the best recruitment and retention strategies applied to pediatric trials.
In the experience of the NCIC CTG, a cancer cooperative group, the screening to enrolment ratio of women with established breast cancer to clinical trials is about 3:2. A breast cancer prevention trial is a new endeavour for us and we are finding that it is very challenging for centres to recruit healthy subjects, as demonstrated by a screening to enrolment ratio of approximately 10:1.

Recruitment strategies commenced with the selection of a diverse group of investigators including oncologists, gynecologists, surgeons, internists, cardiologists and primary care physicians.

The NCIC CTG engaged a public relations firm to brand the trial and create an identifiable logo and name. A recruitment kit was developed containing media trial awareness material such as public service announcements, press release templates, key messages for speakers and media FAQ. The kit also contained participant communication material such as an information video and Q&A for subjects considering participation. The kit also contained participant communication material such as an information video and Q&A for subjects considering participation. A poster and brochure with 1–800 numbers in both Canada and the United States were also developed and printed in large quantities for all sites. All material was produced in English, French and Spanish.

To access potential participants, centres use strategies based on their experiences with other trials, utilizing focused mass mailings, developing community outreach and forming relationships with community organizations. Regular teleconference calls with site coordinators are held to brainstorm ideas, share strategy successes and failures and provide mutual support.

This poster discusses the pros and cons of various recruitment strategies concluding that no one recruitment strategy works for everyone. Centres need to develop a local, multi-level recruitment plan and ensure they have more than one reliable recruitment source.

Retention begins with solid recruitment strategies. Reach and randomize the most “retainable” study participants. But the work does not end at randomization. The resources spent on recruitment only produce benefits if additional focused attention is placed on subject retention throughout the life of the trial. Attrition is high with healthy women on prevention trials and a drop out rate of approximately 10 to 15 percent per annum has been seen on other prevention trials.

The timing and quality of contact with subjects is critical to retention. Repeat contact such as follow-up phone calls and staff support, especially in the first few weeks after recruitment, allows subjects to feel they are partners in research and are making a worthwhile contribution to an important research question. A sense of collaboration may supersede any minor ill effects or inconveniences the subject might experience. Add to this empathetic staff and the subject gains an overall sense of validation and value in their role in the study.

Retention strategies such as milestone give-aways, group appreciation activities like afternoon teas, developing a sense of community through newsletters, bring a buddy promotions and local media attention also help to ensure continued subject interest and satisfaction which will hopefully result in a higher retention ratio. This poster discusses successful retention strategies that are being used. Centres need to foster a relationship with their participants, build trust and create a sustainable retention plan to ensure as many subjects as possible remain on study throughout the 5 year span of this breast cancer prevention trial.

The concept that sample size can be achieved by activating an optimal number of sites is especially true in a re-randomization protocol. NCIC CTG, the coordinating group, targeted 54 sites in Canada and 290 sites in the United States for activation on MA.17R. To address suboptimal activation, a strategy was piloted that included a direct visit by a Medical Science Liaison. Due to insufficient resources, NCIC CTG delegated a team of twenty MSL from the pharmaceutical sponsor to perform this task in the United States.

To maximize data collection and minimize perception of undue influence by the pharmaceutical sponsor, MSL duties were precisely defined: remind the site of the study, confirm and collect contact information, distribute pocket cards, review the process for activation, and identify site-specific questions. At each visit, the MSL completed a standard form and faxed this to the NCIC CTG study coordinator.
Of the 140 sites targeted for visits: 35 (25.0%) were activated, 32 (22.9%) would not be activated (11 had no eligible subjects, 8 had economic concerns or staffing issues, 7 had no cooperative group affiliation, 1 had an IRB issue, 1 joined a competing study), 2 (1.4%) could not be contacted, and 71 (50.7%) are expected to be activated. Despite best efforts, duplication of work occurred in 6 instances where site status was already known.

Extra effort is required to optimize activations from a limited number of sites. Site visits are useful to identify potential obstacles including incorrect contact information, lack of familiarity with the current protocol and activation process, and to gauge site interest.

**P 35**

**REASONS FOR NON-PARTICIPATION IN A CLINICAL TRIAL INVOLVING RE-RANDOMIZATION**

Michael J. Palmer, Wendy Parulekar, Jennifer Broxterman, Paul Goss and Joseph Pater
National Cancer Institute of Canada, Kingston, Ontario, Canada

NCIC CTG trial MA.17R provides a unique opportunity to explore the characteristics of subjects as the identity of every eligible subject is known. On this study, subjects who have taken five years of an oral aromatase inhibitor as adjuvant therapy for breast cancer are re-randomized in blinded fashion to a further five years of the aromatase inhibitor or placebo.

As the majority of eligible subjects are from North America, the status of 798 eligible subjects in Canada and the United States over a three year period was determined. Overall, 395 subjects (49.5%) were randomized, 169 subjects (21.2%) refused, and 74 subjects (9.3%) were ineligible. The status of 160 subjects (20.0%) was pending.

Reasons for refusal include: medication fatigue (14.8%), not interested (14.8%), health concerns (10.1%), old age (6.5%), travel (5.9%), toxicity (4.1%), physician judgment (4.1%), preference for specific treatment (3.6%), inadequate insurance (2.4%), perceived unacceptable risk / benefit ratio (0.6%) and other (2.4%). No reason was provided by 30.7% of subjects.

More subjects from Canada (23.0%) refused because of medication fatigue compared with subjects from United States (10.2%). Only subjects from United States refused because of physician judgment, inadequate insurance, or perceived unacceptable risk / benefit ratio.

Patterns over time, geographic trends, and demographics of subjects categorized as refused or ineligible will be examined. The implications of these results for future re-randomization strategies will be determined.

**P 36**

**CHALLENGES OF CONDUCTING CANCER PREVENTION TRIALS**

Harriet Richardson, Dianne Johnston and Joe Pater
Queen’s University, Kingston, Ontario, Canada

More than half a century of epidemiological and laboratory investigations have resulted in the identification of environmental, lifestyle, hormonal and genetic factors that can influence cancer risk. Cancer prevention strategies, such as anti-estrogen medication for high-risk individuals, are now being evaluated in clinical chemoprevention trials, and have the potential to significantly reduce the incidence of certain cancers.

Nonetheless, there are a number of challenges to conducting cancer prevention trials. The first is that, in general, phase III cancer prevention trials whether based on pharmacological or behavioural intervention, require large sample sizes and long follow-up. This is especially true if reduction in cancer incidence is the primary endpoint, since even in high-risk populations the event rate is low. This in turn means that such trials are very large and expensive and thus far, best accomplished under a cooperative group mechanism, with international scope.

However, an inherent difficulty of conducting cancer prevention trials though a cooperative group mechanism is that most members of clinical trials groups are based in cancer treatment delivery centres. Prevention studies on the other hand often require recruitment of healthy volunteers (albeit at higher than average risk for cancer) from the community. This added complexity requires an orchestrated strategy for expanding the focus of oncology cooperative groups to include cancer prevention and control and to support an expansion into the community setting. Within Canada this means we need to build and improve upon existing network infrastructures (i.e. family physicians, screening clinics) that are necessary to support a platform for future cancer prevention research. These and other methodological considerations will be addressed in the context of conducting cancer prevention clinical trials.

**P 37**

**CHARACTERIZATION OF SUBJECTS WHO MOVE DURING A LONGITUDINAL CLINICAL TRIAL**

Neepa Ray, John Schwarz, Agustin Calatroni, Herman Mitchell and Michelle Walter
Rho, Inc., Chapel Hill, North Carolina, USA

Large scale clinical trials typically involve enormous financial and personnel resources. High rates of study participants lost to follow-up can jeopardize study power and bias study populations in ways that lead to uninterpretable results. Subjects who move during the course of a study appear to be the primary cause of loss to

Clinical Trials 2007; 4: 371–455 http://ctj.sagepub.com
follow-up but surprisingly little is known about the expected rates of moving, the distances they move and factors that may allow one to predict those most likely to move. Studies of asthma which focus on home environments are especially at risk for failure due to losing study participants who move during the course of the research project. Even when study participants move short distances and are not lost to follow-up, the increased effort and cost of re-measuring environmental exposures can be problematic, in addition to the analytic complexities introduced by varying times of exposures and abrupt environmental changes. The Inner-City Asthma Study (ICAS) provides an ideal project for this analysis. It is a longitudinal environmental assessment of 937 inner-city families in 7 major urban areas with data being collected every two months for two years. The goal of this analysis is two fold: first, we will describe the extent of subject relocation; secondly, we will identify the characteristics (environmental, demographic, psychosocial, etc.) of the moving population. Characteristics that discriminate between a stable and a moving population can be incorporated in the study design and allow study personnel to target those most at risk for being lost to follow-up in order to improve retention.

P 38
THE COMPREHENSIVE SICKLE CELL CENTER (CSGCC) SICKLE CELL DISEASE C-DATA PROJECT: ASSESSING POTENTIAL BIAS
Susan Lieff, Marsha McMurray, Melanie Chelednik, Petra Lebeau, Carlton Dampier, Zora R. Rogers, Winfred Wang and Karen Kesler
Rho Federal Systems Division, Inc., Chapel Hill, North Carolina, USA

Despite advances in early detection and treatment of Sickle Cell Disease (SCD), wide phenotypic variability remains. The C-Data Project is an active, comprehensive clinical and HRQoL database of individuals receiving care at 19 clinical US sites, designed to characterize this population and support clinical research. An internet-based electronic data capture (EDC) system is used to collect study data. Limitations of registries include possible bias due to incomplete and invalid data. C-Data reliability and validity are addressed with standard data management methods, real-time edit checks, generation/tracking of queries, investigator quality control procedures, and monitoring visits. Of primary concern is the potential for systematic bias from differential consent, recruitment and enrollment patterns. Greater availability of patients experiencing worse morbidity, ease of enrolling patients with relatively little morbidity, and variation in enrollment practices are significant threats to utility of registry data. A lack of reliable patient population data from participating sites, and for this population nationally, makes it difficult to establish reasonable “denominators” to assess bias. Extensive on-going review of demographic, clinical and genotype data, comparison of these data with those from the Jamaican and CSSCD SCD cohorts, and evaluation of screening/enrollment tracking systems, are techniques currently employed to investigate selection bias from these sources. To date, 2509 subjects have been enrolled. Indicators suggest quality and completeness of data are high; 72% of subjects have complete clinical and QoL data, with only 10% of generated queries unresolved. Approaches to assessing the presence and extent of selection and other bias, and minimizing their impact will be described. Supported by NHLBI U54HL070587.

P 39
AN OVERVIEW OF THE PREREQUISITES, DUTIES AND RESPONSIBILITIES OF AN EFFECTIVE CLINICAL RESEARCH ASSOCIATE
Adrienne E. Brandon
Maryland Medical Research Institute, Baltimore, Maryland, USA

The Clinical Research Associate is responsible for managing and monitoring clinical trial sites, assisting with project specific management, and providing leadership to less experienced clinical trials management staff. The Clinical Research Associate must work in accordance with Good Clinical Practice (GCP) and SOPs. We present an overview of the prerequisites, duties and responsibilities of an effective Clinical Research Associate. In addition, we provide a guideline for ensuring excellence in managing and monitoring clinical trial sites, assisting with project specific management, and providing leadership to less experienced clinical trials management staff.

P 40
AN AUTOMATED APPROACH TO MONITORING ACCRUAL FOR MULTICENTER CLINICAL TRIALS (CTS) ENROLLING PATIENTS (PTS) VIA REMOTE DATA CAPTURE (RDC): A MAYO CLINIC COMPREHENSIVE CANCER CENTER (MCCCC) APPLICATION
Lawrence P. Esser, Michelle R. Mahoney, Diane M. Parkin, Sherry A. Foster, Steven R. Alberts and Daniel J. Sargent
Mayo Clinic, Rochester, Minnesota, USA

Historically, pts enrolled to MCCCC coordinated CTS were obtained via telephone and monitored through manual tracking mechanisms in the MCCCC Randomization Center. Thousands of pts are enrolled annually, to CTS coordinated through the MCCCC. In 2000, the MCCCC began enrolling pts via RDC to improve efficiency.
and accuracy. Removing the requirement of manual tracking introduced the need for automated accrual tracking. Key features of the monitoring system developed are that it is (1) completely automated, (2) based on the data entered by the Statistician and Protocol Development Coordinator prior to study activation, (3) contains both optional and pre-defined default notifications, (4) alerts appropriate personnel via email at key milestones in accrual, and (5) user friendly. In April 2004, the MCCCC Accrual Notification System was implemented. Email notifications are sent, based on recipient names stored within our data base as part of basic protocol information. Optional study specific notifications may be defined by the study team. The form is completed prior to study activation, through a user friendly, web based application. The development of this automated Accrual Notification System has been a useful tool for the monitoring of CTs in multicenter settings, reducing the time necessary to manually (1) verify if a notification is necessary, (2) identify who needs to receive the notification, and (3) contact key personnel. The MCCCC Accrual Notification System has improved the efficiency and productivity of the MCCCC Randomization Center, enabling personnel to focus on other important tasks [eg, triage questions, review protocols/addendum, manual registrations necessary on selected studies not optimal for remote registration (Phase I), maintenance of bottle assignments for double blind studies]. Supported by NIH Grant CA15083–32.

**P 41**

DOES THE ANSWER DEPEND ON THE QUESTION? AN ASSESSMENT OF PRE-FILLING ADVERSE EVENTS (AES) ON CASE REPORT FORMS (CRFS) FOR NORTH CENTRAL CANCER TREATMENT GROUP (NCCTG) CLINICAL TRIALS (CTS)

Michelle R. Mahoney, Daniel J. Sargent, Megan E. Campbell, Brian P. Hobbs, John Kulger, Steven R. Alberts and Jan C. Buckner

Mayo Clinic, Rochester, Minnesota, USA

A subset of AEs are assessed at each patient evaluation for a CT, according to the safety profile known at the time a CT is developed. The NCCTG, a multi-center cancer clinical trial group, pre-fills selected AEs onto CRFs. NCCTG has demonstrated (Mahoney MR, et al, JCO 2005) that 85% (57,033/67,280) of Aes reported were pre-filled onto CRFs, of which, 83% did not occur (Gr 0), and only 1.5% (844/57,033) were Gr 3+. During a CT, new AE signals may prompt an expansion of the AE assessment list. To evaluate the influence of assessing AEs on the CRF reported AE rates, we reviewed a non-random sample of AE data collected from 1/99–6/06 on 74 NCCTG CTs, identifying 13 CTs where AEs were added to CRFs after study initiation. Findings included: (1) 21 of 36 of newly added AEs were never reported prior to adding them onto CRFs; (2) in general, the same AEs were 4-fold (range 0–25) more likely to be reported if pre-filled onto CRFs, (3) routinely tested blood chemistries (eg, SGOT, bilirubin, alkaline phosphatase, creatinine) were 20 times more likely to be reported if pre-filled onto CRFs, and (4) half of the AEs added (10/21) and not occurring prior to their addition onto CRFs, continued to not be observed during a CT. We have also conducted a survey of NCCTG CRAs, to assess the workload impact of pre-filling AEs on CRFs. Overall, our data suggests that there is a significant difference between the rates of Aes reported if specifically requested in the CRF. A prospective study is planned to formally evaluate this observation. Supported by NIH Grant CA25224.

**P 42**

USING STANDARDIZED PATIENTS TO PILOT SCREENING VISITS IN CLINICAL TRIALS

Lynn E. Kunkel¹, Holly Fussell², Colleen Shannon-Lewy² and Bentson McFarland²

¹Oregon Health & Science University

²Oregon Health & Science University Department of Psychiatry, Portland, Oregon, USA

Standardized patients are used widely in medical education to assist in training and evaluating clinical skills. This qualitative analysis reports on an innovative strategy that uses a standardized patient to pilot patient screening and intake processes for two clinical trials conducted in the National Institute on Drug Abuse Clinical Trials Network. The standardized patient roles, originally created as substance abuse clients, were modified to meet study inclusion/exclusion criteria. The standardized patient acted as a drug dependent individual seeking treatment and “walked” through the study intake process, including being interviewed by research assistants and study nurses. Debriefing staff and the standardized patient led to modifications to the clinical implementation of the studies and to increased training for staff. The changes assisted in the success of study implementation with randomized participants.

Overall, practice with a standardized patient increased staff confidence in the participant flow and improved understanding of how the data collection would occur with “real” study participants. Although originally designed for clinical purposes, the standardized patient role was easily modified and applied to the clinical trials.
One of the major challenges in clinical trials involving radiation therapy (RT) is to identify and correct protocol treatment deviations on a timely basis since variation in treatment delivery may impact outcomes such as disease control, toxicity (acute and long term) as well as quality of life. The RT quality assurance (QA) is of paramount importance to ensure that any outcome differences (or lack of) are due to the treatments as defined in the protocol. The objective of this study is to review the existing use of QA with an emphasis on RTR in trials involving RT, the manner in which they are reported, and the reported impact on protocol deviations. Based on the findings a minimum acceptable QA will be recommended.

Published phase III trials involving RT from 1996–2006 will be reviewed. Points of interest include: type of QA used, credentialing versus RTR, defined criteria of minor and major protocol deviations, percentage of deviations mandating a change in treatment plans, adherence with the RTR recommendations and the impact of QA or RTR on final treatment assessments.

The QA methods used in protocols will be compared and an effective score will be defined and reported. The percentage of deviations captured will be reported.

The DCCT and its EDIC multi-center longitudinal follow-up study have achieved many of their goals in the last 24 years by demonstrating the beneficial effects of intensive therapy in reducing the risk of microvascular and cardiovascular complications in Type 1 diabetes. The DCCT/EDIC study has retained 93% of the original DCCT cohort (96% of survivors) as of 2005. Maintenance of stable methods and calibration of new methods against older ones are critical in this long-term study. For example, a recent EDIC evaluation of cognitive function was performed, 12 years after its last performance at the end of the DCCT, using the same comprehensive test battery. Similarly, the neurological protocol last performed in the DCCT in 1993 had to be repeated in 2006, again using methods identical to those used during the DCCT. Changes in methods that require calibration include: transitioning between assay methods for HbA1c, changing reading centers and from fundus photography to digital photography, and shifting from a 4 hr urine collection to measure albumin excretion rate (AER) to a spot urine collection to measure the albumin creatinine ratio (ACR). Maintaining stability in study tests, and comparability between newer and older methods, is essential to the conduct of long-term studies. For example, a recent EDIC evaluation of cognitive function was performed, 12 years after its last performance at the end of the DCCT, using the same comprehensive test battery. Similarly, the neurological protocol last performed in the DCCT in 1993 had to be repeated in 2006, again using methods identical to those used during the DCCT. Changes in methods that require calibration include: transitioning between assay methods for HbA1c, changing reading centers and from fundus photography to digital photography, and shifting from a 4 hr urine collection to measure albumin excretion rate (AER) to a spot urine collection to measure the albumin creatinine ratio (ACR). Maintaining stability in study tests, and comparability between newer and older methods, is essential to the conduct of long-term studies. We propose several strategies to maintain stability to those used during the DCCT. Changes in methods that require calibration include: transitioning between assay methods for HbA1c, changing reading centers and from fundus photography to digital photography, and shifting from a 4 hr urine collection to measure albumin excretion rate (AER) to a spot urine collection to measure the albumin creatinine ratio (ACR). Maintaining stability in study tests, and comparability between newer and older methods, is essential to the conduct of long-term studies. We propose several strategies to maintain stability in study measures and to facilitate the transition from older to newer methods, when necessary.

Central units are used in multi-center studies to provide standardization and technical expertise needed to analyze major outcomes. Examples of central units, usually funded through the Coordinating Center (CoC), include electrocardiogram (ECG) reading centers, fundus photo grading centers, and central biochemistry laboratories. Often the sponsor requests that the CoC issue subcontracts to the central units rather than funding them directly. To assure high quality analysis of study outcomes, the CoC aims to establish a comprehensive performance monitoring system. Such a system requires that the CoC (1) clearly communicate requirements to the central units; (2) carefully monitor performance; and (3) provide timely feedback and pursue corrective actions when necessary. The CoC and the central unit must agree on the work requirements formally communicated in the detailed work scope, including a timeline for each deliverable. To monitor performance in a systematic way, the CoC uses a quarterly checklist, customized to each central unit and reflective of the work scope. Each quarter, the CoC staff members knowledgeable about performance areas complete specific sections of the checklist to evaluate the central unit. The sections address components such as data management, contract administration, study design, and quality control. The quarterly performance monitoring system results in regular feedback to the central units and provides a guideline for CoC’s corrective actions. Corrective actions include initiating more frequent communications and offering additional assistance. This system helps to reinforce excellence within central units critical to the success of the study.
SPS3 is an international multicenter, randomized clinical trial with three main objectives including: 1) Compare clopidogrel/aspirin vs. aspirin for prevention of recurrent stroke and cognitive decline; 2) Compare “usual” vs. “intensive” blood pressure lowering in patients with recent S3 on recurrent stroke, cognitive decline and quality of life; 3) Identify and characterize risk factors for stroke recurrence and cognitive decline in patients with recent S3. The efficient and secure reporting of Serious Adverse Events (SAEs) is of primary importance in Phase III clinical trials, requiring methods that are timely and reliable. We will illustrate our procedures of monitoring SAEs using open source email, HTML and FoxPro programming, thereby creating an innovative web-based structure. In utilizing the structure to monitor the initial and follow-up event data pertinent to the assessment of SAEs, we have developed a process that is accessible and convenient to the Clinical Coordinators and the Medical Safety Monitor (MSM). Clinical Coordinators report the SAEs by entering pertinent information into their local data entry systems, which is then written to a data table in the FoxPro database. Reports of four categories of events are automatically generated and forwarded by the SPS3 Statistical Center (SC) to the MSM immediately upon receipt. The MSM is closely involved in the system’s design, therefore providing the SC with invaluable perspectives of what is required to maintain a successful enterprise. Design challenges contribute to both positive and negatives aspects of maintaining a web-based system. With the addition of new features and system upgrades, our web-based system is successful in the accurate account of SAE reporting and the monitoring of patient safety.

Coordinating a Multi-Site, Multi-Study Data Safety Monitoring Board: Lessons Learned

Jay Johnson and Dianna M. Milewicz
University of Texas, Houston, Texas, USA

To ensure Controlled Clinical Trials (CCTs) balance rigorous scientific standards with patient safety, the use of Data Safety Monitoring Boards (DSMBs) is increasingly common. To this end, the National Institute of Health issued guidelines requiring oversight and monitoring by DSMBs of all intervention studies to ensure the safety of participants and the validity and integrity of data. Typically, a DSMB oversees a single study in one geographic area or at multiple sites. The purpose of this presentation is to describe and depict the lessons learned from an atypical DSMB, that is, a DSMB charged with overseeing research participant safety for several different studies being conducted at several different sites. Specifically, this presentation depicts how practical organizational, communication, materials delivery, maintenance, and logistical issues and challenges were addressed. A theme emphasized throughout this presentation is that, despite the wide geographic dispersion of DSMB members and their diverse scientific backgrounds as well as differences in studies monitored, centralized safety monitoring is important in promoting safety and precautionary measures while sustaining efficiency in study implementation.

Inter- and Intra-Reader Variability in Scoring of Cardiovascular Diagnostic Images in Clinical Trials

James R. Johnson
Campbell University School of Pharmacy, Morrisville, North Carolina, USA

Cardiovascular clinical trials utilizing diagnostic imaging modalities to assess clinical outcomes as the primary efficacy endpoint require application of statistical methods to address inter- and intra-reader variability in the interpretation of the images. The design of these trials necessitates the use of multiple independent readers to score images for the target endpoint. Trained readers often times use ordinal, yet subjective, scoring systems in their interpretation that have inherent reader biases that must be addressed. In order to assess the validity and interpretability of the diagnostic modality, as well as the scoring systems employed, methods must be included in the clinical trial design that reduces potential biases and adequately addresses intra- and inter-reader variability. This paper presents trial design considerations to address intra- and inter-reader variability inherent in diagnostic imaging trials. A case study is presented with cardiovascular myocardial perfusion imaging addressing design issues, blinding and randomization methods for independent scoring, blinded-rereads, trigger points for adjudication of independent assessments, and random selection for an independent 3rd party over-read. Statistical methods applied to address concordance within and between readers include use of McNemar’s and regression models to understand and quantify inherent reader variability.
P 49
BINOMIAL CONFIDENCE INTERVALS FOR A SINGLE PROPORTION
James F. Reed III
Lehigh Valley Hospital & Health Network, Allentown, Pennsylvania, USA

Introduction The construction of a confidence interval for a binomial parameter is one of the most basic analyses in statistical inference. Despite the known poor performance of the Wald forms, they continue to dominate in textbooks and in published literature. We investigate the behavior of alternative binomial confidence interval methods in constructing confidence intervals for a single proportion for combinations of n and p that satisfy the typical textbook warning (Wald-z should only be used when n · min (p, 1-p) ≥ 5).

Methods Computational methods included W-z, W-c, W-t, W-q, Clopper-Pearson, Score, Score-c, Agresti-Coull, Borkowf-z, and Borkowf-t and were evaluated for n = 50 and for p = 0.1, . . . , 0.9, 0.001. The two standard measures of performance for binomial confidence intervals are the coverage probability, C (π|n, α) and mean width, M (π|n, α).

Results Coverage probability plots demonstrate that the W-z, W-c, W-t, W-q, and Blythe-Still methods are poor performers as they seldom reach the nominal level. The Clopper-Pearson and Score with continuity correction methods are overly conservative as they generally exceed the nominal level. The Score and Agresti-Coull coverage methods are nearly nominal for π ∈ [0, 1]. The W-z and W-c methods both behave poorly in terms of zero width intervals and overshoot. The Clopper-Pearson “exact” method is the most conservative.

Discussion The Clopper-Pearson and the Score methods are better binomial confidence intervals than either W or WCC. Other better alternatives include Wilson’s Score with continuity correction, the Agresti-Coull, and the Borkowf-z methods.

P 50
UNIQUE APPLICATION OF KAPPA PRINCIPLES TO A LARGE-SCALE ETHNOGRAPHIC INTERVIEW INITIATIVE EMPLOYING MULTIPLE CODES AND REVIEWERS
Sharon R. Kimmel, Lynn Dietrick and James Reed
Lehigh Valley Hospital & Health Network, Allentown, Pennsylvania, USA

This presentation reviews sample selection and kappa processes used to measure content and internal validity of multiple ethnographic interviews. The initiative yielded 225 transcript responses emergent coded using multiple (n = 4) reviewers. Passages contained multiple codes. Sample size principles needed to ensure representation and random sampling were used to select passages for review. Kappa statistic principles were used to measure strength of agreement within passages while accommodating for non-voting reviewers and multiple codes. This technique differs from common Cohen kappa in that multiple codes were applied by multiple reviewers for each passage as opposed to one code per reviewer.

P 51
BINOMIAL CONFIDENCE INTERVALS OR JUST PLAIN LUCK
James F. Reed III
Lehigh Valley Hospital & Health Network, Allentown, Pennsylvania, USA

Introduction In recognition that the actual coverage probability of the familiar Wald-z binomial confidence interval is poor for p near 0 or 1, textbooks include a warning that Wald-z should only be used when n-min (p, 1-p) ≥ 5. Our objective is to demonstrate that there are combinations of n and p that satisfy this warning where the coverage probability is substantially lower than advertised and that the user may really be lucky or unlucky. Methods: Alternative binomial confidence interval methods include adjusted Wald methods, the “gold standard” Clopper-Pearson, Wilson’s Score, and Wilson’s Score with a continuity correction. The coverage probability functions for these alternative methods are evaluated for p = 0.1, 0.5, 0.1 for n satisfying the traditional “rule”.

Results When p = 0.1 and n = 106, the actual coverage probability of the nominal 95% W, CP (π| n, α) = 0.9515, but CP (0.1 | 107, 0.05) = 0.9098. When n ∈ [50, 150], CP (0.1 | n, 0.05) > 0.9500 in only two instances - when n ∈ [106, 120]. This erratic behavior of W continues for CP (0.5 | 17, 0.05) = 0.9510, but CP (0.5 | 18, 0.05) = 0.9037.

Discussion The coverage probability is far more erratic as a function of n than could be expected. This behavior does not disappear even when n is relatively large. The oscillation of the coverage probability shows that there are a large number of combinations of p and n where the corresponding CP is considerably smaller than the nominal level.
P 52

THE ESTIMATION OF SENSITIVITY AND SPECIFICITY OF CLUSTERED BINARY DATA: AS APPLIED TO CONTRAST-ENHANCED MULTI-DETECTOR ROW SPIRAL COMPUTED TOMOGRAPHY CORONARY ANGIOGRAPHY
William F. McCarthy, Douglas R. Thompson and Bruce A. Barton
Maryland Medical Research Institute, Baltimore, Maryland, USA

Contrast-enhanced multi-detector row spiral computed tomography (MDCT) has been introduced as a method for non-invasive visualization of coronary artery stenosis. To determine the diagnostic accuracy of MDCT coronary angiography, as compared to the “gold standard” invasive coronary angiography, sensitivity and specificity are estimated (95% CIs). Three separate levels of estimation are computed: at the patient level, at the coronary vessel level, and at the coronary segment level. We present a methodology for the estimation of sensitivity and specificity that takes into consideration the clustering (nesting) effect associated with the nesting of segments within vessels and vessels within patients.

P 53

STATISTICAL APPROACHES TO ESTABLISHING BIOEQUIVALENCE
William F. McCarthy, Nan Guo and Bruce A. Barton
Maryland Medical Research Institute, Baltimore, Maryland, USA

An important aspect of a pharmacokinetics (PK) study is the assessment of how much of the active constituents of the drug reaches its site of action. Since this type of assessment is difficult to make directly, the concentration of the drug that reaches the circulating bloodstream is taken as a surrogate. This concentration of the drug in the blood is referred to as its bioavailability. Two drugs that have the same bioavailability are termed bioequivalent. Following FDA Guidelines, the statistical analysis should be based on the non-compartmental PK parameters AUCinf (Area Under the Curve from time 0 to infinity) and Cmax (maximum concentration) derived from the drug concentration-time curve. We present three statistical methods for assessing bioequivalence: Average Bioequivalence (ABE), Population Bioequivalence (PBE), and Individual Bioequivalence (IBE). In addition, we make a comparison of the regulatory requirements for bioequivalence between American (FDA), Canadian (TPD) and European (EMEA) agencies.

P 54

A BAYESIAN APPROACH TO A PHASE III STUDY IN THE TREATMENT OF ACQUIRED IMMUNE DEFICIENCY SYNDROME ASSOCIATED CRYPTOCOCCAL MENINGITIS
Tracy Nolen Dennis Wallace Louise Zimmer and Peter Pappas
Rho Federal Systems Division, Inc., Chapel Hill, North Carolina, USA

The Bacteriology and Mycology Study Group has completed an open-label phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of AIDS associated cryptococcal meningitis (BAMSG 3–01). The primary objective of this study was to determine if the safety and efficacy profile of combination therapy supported moving forward with a phase III study. A subject was considered to have a successful primary efficacy endpoint if, at study day 14, the subject was alive, neurologically stable or improved, and culture negative for cryptococcal meningitis. Preliminary results from this study suggest that the two major obstacles in implementing a phase III trial will be identifying and enrolling the necessary number of subjects diagnosed with AIDS-associated cryptococcal meningitis and obtaining the lumbar punctures needed for the efficacy endpoint used in the phase II study. This presentation explores the use of both a Bayesian study design and a surrogate endpoint for the phase III trial. Implementing a Bayesian hierarchical model, with the prior distribution based on the results of BAMSG 3–01, will utilize the statistical information gained through the phase II study to reduce the required sample size for a Phase III study. As part of our investigation, we will determine whether the prior distribution of a composite endpoint based on mortality and neurological status alone supports the use of this simplified endpoint in the phase III trial. This approach would thereby eliminate the need for performing lumbar punctures. By utilizing a Bayesian approach and surrogate endpoint, we will increase the feasibility of a phase III study.

P 55

RELATIONSHIP BETWEEN ALLERGEN EXPOSURE AND ASTHMA MORBIDITY
Jeremy J. Wildfire and Herman Mitchell
Rho, Inc., Chapel Hill, North Carolina, USA

Background  Asthma morbidity is frequently triggered by allergic reactions in asthmatic children. As such, reducing exposure to harmful allergens is often a key component of asthma treatment. To better define clinical guidelines for reducing allergen exposure, it is critical to understand the relationship between allergen exposure and
Participation of subjects on multiple clinical trials: the National Cancer Institute of Canada Clinical Trials Group MA.20 experience

Shauna R. McGill, Beverly Koski, Timothy Whelan and Wendy R. Parulekar

National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada

Participation of a single study subject onto multiple clinical studies is a common issue for clinical trialists. This is especially true in cancer treatment studies involving subjects with relatively good prognoses where duration of follow-up is measured in years. Important considerations include eligibility criteria of the studies, ability to comply with protocol mandated procedures, impact of participation of multiple studies on the outcomes of interest, potential imbalances of enrollment of patients on one particular arm of a study, and patient fatigue with respect to protocol driven investigations/visits. We describe our experience with NCIC CTG MA.20 (Phase III Study of Regional Radiation Therapy in Early Breast Cancer), which examines the impact of regional radiation on overall survival in patients treated with breast conserving surgery. Secondary endpoints include disease free survival, local regional and distant disease free survival and toxicity. Quality of life and cosmetic outcomes are also measured. This is an international study with Canadian, American and Australian participation.

The NCIC CTG MA.20 trial team has established a decision process for allowing study subjects entry onto other studies. This includes targeted review of other protocols for eligibility, type of study (therapeutic versus other), schedule of follow-up and investigations, consent. The Study Chairs of all involved trials are contacted for approval prior to allowing enrollment on multiple studies whenever possible. Finally, a study specific log is maintained for future reference.

http://ctj.sagepub.com

Clinical Trials 2007; 4: 371–455
To date, NCIC CTG MA.20 has accrued 1783 patients (target sample size 1822). Participation on 49 other studies was allowed, affecting 235 patients. Participation was not allowed for 5 studies. Categories of approved studies include treatment, supportive care, genetic testing, imaging and tissue banking.

P 58
DEVELOPMENT OF AN ATOPIC DERMATITIS MULTI-SITE SUBJECT REGISTRY
Jamie T. Reese, Robert Holliday, Susan Lieff, Lisa Beck and Kathleen Barnes
Rho, Inc., Chapel Hill, North Carolina, USA

Individuals with atopic dermatitis (AD) are at risk for eczema vaccinatum (EV) from the smallpox vaccine. The primary goal of the Registry is to develop a large database of well-categorized and defined individuals with AD and healthy controls to support subsequent protocols of immune processes and collect demographic and biological data from these individuals that will be used to characterize relevant biomarkers. These biomarkers may be used identify individuals at high risk for EV from receiving the smallpox vaccine during a large-scale vaccination campaign. Registry development requires a high level of standardization to achieve objectives from multiple investigational sites. The Coordinating Center facilitated the development of standard definitions for AD, history of AD, nonatopic controls, atopic dermatitis with eczema herpeticum and other related conditions for use across all centers. In a collaborative effort between all sites and the Coordinating Center, a Material Transfer Agreement (MTA) was created and approved, allowing biological samples to be exchanged between sites. A standard procedure for photographing subjects with rare conditions was customized to meet the study requirements. Within two years a multi-site Registry of subjects diagnosed with AD and other related conditions has been successfully created and is actively recruiting subjects.

NIH/NIAID Contract HHSN266200400033C and HHSN266200400029C

P 59
THE DESIGN AND IMPLEMENTATION OF AN ELECTRONIC LABORATORY SPECIMEN TRACKING SYSTEM AS A TOOL IN COLLABORATIVE CLINICAL RESEARCH AND MULTICENTER CLINICAL TRIALS
Lynna Woods, Rose Wilson and Susan Lieff
Rho Federal Systems Division, Inc., Chapel Hill, North Carolina, USA

Collaborative efforts among multiple medical centers are often necessary to address important clinical questions. The National Heart, Lung, and Blood Institute (NHLBI) Comprehensive Sickle Cell Centers (CSCC) program consists of 10 Centers and a Statistics and Data Management Center (SDMC), and supports collaborative multi-center clinical trials that focus on improving treatments for individuals with sickle cell disease. To efficiently conduct such multi-center clinical trials, the SDMC has made significant efforts to increase the accuracy of data entry, data collection, and to streamline the transfer of patient specimens between clinical research sites and central laboratories. RhoLAB™, a sophisticated electronic laboratory tracking system, has been developed by the SDMC for use in “An Extended Phase II Study of Decitabine in Subjects with High Risk Sickle Cell Disease,” one of the NHLBI CSCC sponsored clinical trials. The RhoLAB™ system allows sites to track and ship blood specimens, and sends electronic notifications to investigators when results are available. RhoLAB™ provides detailed information to central laboratory investigators about specimen collection and shipment. In addition, recent upgrades to the RhoLAB™ system allow central laboratory investigators to ship and track specimens from one central laboratory to another; and the upgraded system provides investigators with detailed information about shipments, including the laboratory or site from which a specimen originated. These capabilities, combined with the use of customized laboratory collection kits, bar code scanners, and specimen labels, provide for maximum accuracy in entering data and tracking specimens for the duration of the clinical trial.

Supported by NHLBI U54HL070587.

P 60
ORGANIZATIONAL SYSTEM FOR PROCESSING STUDY MATERIALS IN A MULTICENTER TRIAL
Robin L. Zeffiro, Alissa Janis, Preethy Kolinjivadi and Susan Drilea
George Washington University, Rockville, Maryland, USA

The HEALTHY study is a 3-year cluster design trial involving 42 middle schools at 7 field centers nationwide. Production and delivery of study related materials is confounded by great variability across school and center in terms of quantities, deadlines, and other specifications. An organizational tracking system was needed to coordinate and track production and distribution procedures. The coordinating center developed a master materials database as an Excel spreadsheet to meet this purpose. The database is updated and posted to the internal study website.

Using the spreadsheet, the study group can access information including the specifications, shipment arrival date, postal tracking number, and quantity to help prepare for the arrival of materials and anticipate the amount of storage space that the materials will require. In addition, study group members can check the stage of development.
for a material, including where it is in the study group review and approval process. Delivery confirmations are logged so the field center project coordinator is able to confirm if a shipment has arrived. The database is an invaluable tool for the coordinating center as well. Embedded formulas are used to automatically compute quantities and time to deadline. Also, having easy access to the stage of development and delivery notifications helps the coordinating center alert the sites of upcoming deliveries and production of materials. The coordinating center is able to remind committees of deadlines to approve materials so that production and delivery are on time.

P 61
OPTIMIZING THE PRODUCTIVITY OF A CLINICAL TRIAL’S STATISTICAL ANALYSIS AND MANUSCRIPT PREPARATION THROUGH THE DEVELOPMENT OF AND ADHERENCE TO BEST PRACTICES
Heather J. Hoffman
George Washington University, Rockville, Maryland, USA

The primary objective of a statistical coordinating center is to manage the design, execution, and analysis of multi-center clinical trials and epidemiological studies that yield results of the highest scientific integrity and biostatistical standards. Undoubtedly, the success of a coordinating center in attaining this goal and of the collaborative group in efficiently delivering a final outcome to the scientific community depends on having an optimal set of predefined techniques, commonly referred to as “best practices”. Such methods, however, are not set in stone; rather, they are updated periodically to encourage continuous learning and improvement. We present our evolving best practices for statisticians working with writing groups that include guidelines ranging from the development of the analysis plan to publication of the manuscript. Our best practices focus on development and upkeep of the analysis plan; the recommended order of analyses and decision points; in-person, conference-call and email interactions with writing groups and writing group chairs; preparation of manuscript text, tables and figures; and finally manuscript submission and publication. In particular, we recommend eliciting participation from all writing group members when developing the detailed analysis plan and formulating clearly defined hypotheses, requiring that writing groups adhere to the analysis plan and maintain communication within the writing groups. As Frederick Taylor once proclaimed, “Among the various methods used in each element of each trade there is always one method which is quicker and better than any of the rest.” This method reflects the discovery process resulting in our recommended best practices.

P 62
IMPLEMENTATION OF A PROJECT MANAGEMENT TOOL WITHIN THE ENVIRONMENT OF INVESTIGATOR INITIATED TRIALS
Jacek Hajda, Andreas Eisenmenger, Andreas Klinger and Steffen Luntz
Coordination Centre for Clinical Trials, Heidelberg, Germany

Investigator initiated trials (IITs) frequently show some deficits in respect of scheduling of capacities, costs, and timelines. This phenomenon is apparently due to a pronounced workload for clinicians coping with medical care, teaching and research. Our centre was launched to support clinical investigators at the University Heidelberg. We report about our experiences in the planning of an implementation of a commercial project management tool (PMT) within environment of IITs.
At the first stage we aim at introduction of PMT in our centre. This process will consist of two phases. We outlined the scope of PMT use for each particular function, e.g. study coordinator, clinical monitor, etc. and specified a project structure plan and a time schedule for the realization. Furthermore, we defined unequivocal criteria to pick out two IITs for the first, test phase. During this phase the KKS staff in charge of the selected IITs will perform all activities related to the study planning and controlling by use of PMT. After predefined milestones have been reached we will carry out an interim evaluation of the handling of PMT in our daily work. If required, some adaptations will be performed and all employees will undergo a user training. Thereafter, the second, i.e. completion phase will be launched. All planning and controlling tasks at our centre will be based on PMT exclusively. An endpoint evaluation will then be done by comparing our observations with the predefined success criteria. Final adjustments will be carried out if necessary.
Finally, the clinicians will get involved in the use of the tool in order to increase their efficiency in research planning and controlling.

P 63
OPTIMIZING LOGISTICS UNDER A THREE LEVEL ADMINISTRATION SYSTEM: COORDINATION OF THE FOCAL SEGMENTAL GLOMERULAR SCLEROSIS (FSGS) TRIAL
Milena Radeva, June McMahan, and Jennifer Gassman
Cleveland Clinic Foundation, Cleveland, Ohio, USA

The FSGS Study is a multicenter, prospective, controlled, open label NIH-funded randomized clinical trial testing whether cyclosporine (CSA) or mycophenolate mofetil (MMF) and oral dexamethasone will cause a participant’s
Steroid-resistant FSGS to go into remission, defined by a specified reduction in protein to creatinine ratio in participant’s first morning urine. Study outcome is assessed at weeks 26, 52, and 78. FSGS is a rare disease, and enrollment in the study is difficult, especially because of previous exposure to CSA or MMF. A 3-level structure was implemented to maximize the efforts to accrue sufficient number of participants in the trial from the US and Canada. Data Coordinating Center (DCC), 3 Core Coordinating Centers (CCC) and over 130 Participating Sites (PS) each affiliated with one CCC. The study medications are distributed by a Drug Distribution Center upon request by DCC. The blood and urine tests are performed by a Core Laboratory. Biological samples are submitted to NIH Biosample and DNA Repositories. The study uses distributed data entry system. The complexity of the study protocol and study structure and rarity of the disease present specific significant challenges in the study communication and logistics. The DCC has developed a daily feedback information system from the Core Lab to the PSs and CCCs. The Cores receive daily reports on the study activities at their PS electronically. The study team has developed 2 websites. One of them, www.fsgstrial.org, is maintained by one CCC and is directed to potential participants and investigators. The other website is maintained by DCC and contains the study documentation and database links. We issue a quarterly newsletter to update PSs about the study. Sites that enrolled participants receive a “Tip of the Week” reflecting common issues reported by the coordinators. The Core coordinators keep monthly phone contact with each of the sites assigned to their cores. An Annual FSGS Investigators Luncheon is held at the ASN meetings, the Steering Committee meets twice a year, and study coordinators meet annually.

**P 64**

**Utilization of Pediatric Health Related Quality of Life (HRQoL) Data from the Comprehensive Sickle Cell Centers (CSCC) C-Data Project**

Carlton Dampier, Susan Lieff, Marsha McMurray, Karen Kesler, Winfred Wang and Zora R. Rogers  
DrexMarian Anderson CSCC St. Christopher’s Hospital, Philadelphia, Pennsylvania, USA

Sickle Cell Disease (SCD) is a genetic disorder of hemoglobin structure with complex disease manifestations, where the few available therapies require prolonged treatment and cure is usually unattainable. HRQoL evaluates the impact of treatment or disease processes on emotional, social and physical well-being, from a patient’s or patient’s perspective. C-Data is an active, comprehensive clinical and HRQoL database of individuals with SCD receiving care at 19 US clinical sites. Subjects < 18 years of age complete the PedsQL™; parents complete a proxy report. To date, 810 subjects, ages 5–18 years, have complete clinical and HRQoL data. Preliminary analyses suggest adequate internal consistency/reliability, except for some subscales in the youngest age group. Parents, but not children, reported increasing sleep-related dysfunction with increasing age (p < .001); children, but not parents, reported increasing difficulty with social functioning with increasing age (p < .001). The number of unscheduled visits for pain was significantly (p < .01) inversely related to QoL scores on most subscales. Initial multivariate analyses of potential disease-modifying therapies in the previous year paradoxically indicate that patients receiving transfusion reported significantly lower QoL on many subscales, while hydroxyurea usage did not appear to significantly affect QoL. Many of these initial findings underline methodologic difficulties of using patient outcome data, but provide a wealth of information about disease impact on daily functioning that will likely inform future disease-specific HRQOL instruments. HRQOL validation strategies, and possibilities and limitations in the application of these data to design of therapy trials, will also be presented.

Supported by NHLBI U54HL070587.

**P 65**

**Adjudication Committees: Reported Use and Process in Randomised Controlled Trials**

Agnes Deschartres, Isabelle Boutron, Carine Roy and Philippe Ravaud  
INSERM, Paris, France

**Context** Adjudication committees (ACs) are recommended as a quality assurance method to assess clinical events in Randomized Controlled Trials (RCTs). However, little information has been published on the functioning of such committees.

**Objective** To assess the rate of reporting ACs and to systematically review the process of adjudication reported in RCTs published in high impact factor journals.

**Design**: We searched MEDLINE for reports of RCTs reporting clinical events endpoints and published between January 1, 2004 and December 31, 2005 in the 5 highest impact factor journals. Main Outcome Measures: Data extracted by use of a standardized form concerned the reporting of ACs and the description of the process of adjudication.

**Results** A total of 314 articles were selected in which 118 ACs were identified in 105 articles (33.4%). ACs were reported in 81.3% of cardiovascular trials, 28.6% of neurological trials and 15.4% of hematologic or oncologic trials. Among the trials where the intervention was not delivered in a blind fashion, 34.6% reported an AC. Of the 118 ACs reported, 115 (97.5%) were described. The method for selecting cases to be adjudicated was reported for 104 ACs (89.7%) and consisted mostly of events identified by site investigators (n = 97, 93.3%). Description of information provided to the AC was reported for 56 ACs (47.4%). The composition of the AC was reported for 105 ACs (89%). The reviewing process was described for 34 ACs (28.8%).
Conclusions  Our findings highlight the need for defining standardized criteria concerning the assessment of clinical events by ACs.

P 66
ASSESSING THE RELIABILITY OF REPORTING ADVERSE EVENT ATTRIBUTION: A NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS GROUP EVALUATION OF A PHASE I/III PLACEBO CONTROLLED TRIAL (NCIC CTG PA.3)
Barbara Graham, Dongsheng Tu, Marlo Whitehead, Dora Voskoglou-Nomikos, Wendy Parulekar and Joseph Pater National Cancer Institute of Canada, Kingston, Ontario, Canada

Attribution provides valuable information for the interpretation of adverse event (AE) data reported in clinical trials including reporting requirements of serious adverse events (SAEs), and establishing the safety profile and dose levels for newer agents. However, this information is often difficult to obtain, adding time and cost to the clinical trial process. Given the importance of the decisions made based on attribution, the reliability and consistency of reporting was considered for a phase I/III placebo controlled study of gemcitabine +/- Tarceva in patients with advanced or metastatic pancreatic cancer (NCIC CTG PA.3). Attribution was collected according to Common Toxicity Criteria Version 2.0 (CTC V.2) and was considered “not related” (unrelated or unlikely) and “related” (possible, probable or definitely). Inter-rater reliability over time for the same event will be explored and compared between the placebo and active treatment arm. The reliability of attribution will be compared in the phase I and phase III portions of the trial to determine if differences in reliability of attribution exist depending on the extent to which the toxicity profile is known.

In the phase III portion of the trial, the reliability of the “known” AEs of the investigational agent (Tarceva) will be compared to those that are attributed but are “unknown”. Finally, the severity of the AE will be considered to determine if the seriousness of the event affects the reliability of the attribution reporting. The value of collecting this data and the potential implications for clinical trials research will be discussed.

P 67
ANALYSIS OF ADVERSE EVENTS IN CLINICAL TRIALS USING DATA MINING
Jeng-Jong Pan1, David Liu1 and Sheng-Tun Li2
1National Institute on Drug Abuse, Bethesda, Maryland, USA
2National Cheng Kung University, Tainan, Taiwan

One research topic in the secondary analysis of clinical trials data is the detailed investigation of interactions between participant characteristics and special outcomes. For instance, analyses that examine whether certain people may be more likely to experience adverse effects related to study medications could be of great interest to healthcare providers and their patients. In order to outline the general profiles of study participants who experience adverse medication effects, data mining can be applied to analyze adverse events data. Data mining is a technique to uncover hidden patterns and rules that are useful for classification.

In this study, we focus on (1) merging of data on demographics, physical examination findings, medical history, vital signs, medication dosage, and adverse events, (2) extraction of classification rules, which can be used to predict whether a new patient will experience adverse medication effects, (3) balancing the confidence of rules and the number of rules, (4) pitfalls in the interpretation of rules, (5) analyses of accuracy, sensitivity, and specificity, and (6) integration of statistics and data mining for better interpretation. The data used in this study are from the research “Buprenorphine/Naloxone versus Clonidine for Inpatient/Outpatient Opiate Detoxification,” a trial sponsored by the Center for the Clinical Trials Network at the National Institute on Drug Abuse. These data, which are compliant with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards, are available for public use (see http://www.nida.nih.gov/CTN/Data.html).

P 68
VARIATIONS IN ACTIVATION TIMES OVER TIME AND ACCORDING TO TRIAL TYPE: THE NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS GROUP EXPERIENCE
Patti S. O’Brien, Corey Willman, Andrea Hiltz and Joseph Pater
National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, Canada

The experience of staff at NCIC CTG is that it is taking longer to locally activate centres following study central activation than in previous years. This has had an impact on the timely completion of randomized clinical trials. The ethics and regulatory database at NCIC CTG contains central activation (CA) and local activation (LA) dates for all Canadian sites for all studies in which it participated from 1992 until 2006. This wealth of data provides the opportunity to explore questions related to the interval between CA and LA. Our hypothesis is that the time from CA to LA of the first Canadian site for all NCIC CTG led trials has increased over time from 1992 to 2006. We also hypothesize that time from CA to LA of the first Canadian site varies across different trial characteristics. Preliminary results indicate there were substantial variations in activation times over time. NCIC CTG led studies that were centrally activated between 2004 and 2006 took, on average, more than twice as long to locally activate...
Increasing rates of healthcare-associated antimicrobial resistant bacterial infections such as MRSA and VRE are a major public health concern. The Bacteriology and Mycology Study Group conducted a trial of strategies to reduce transmission of antimicrobial resistant bacteria in intensive care units (STAR*ICU). The control strategies could only be implemented through an ICU-randomized design. The ICU (rather than patient) was the planned unit of analysis. Data collection for the primary outcome of incidence density of colonization with either MRSA or VRE was straightforward; but collecting the information on patient and ICU characteristics needed to elucidate mechanisms of action and aid in comparing colonization incidence across the 2 arms was more complicated. Creative sampling strategies were implemented to allow comprehensive patient characterization (e.g., process data such as use of systemic antimicrobials, invasive devices, parenteral nutrition, total number of aerobic bacterial cultures collected) and assessment of ICU staffing and staff compliance within study resource limitations. For example, limited data were collected on subjects with an ICU LOS of less than 3 days as those subjects had a limited impact on the primary endpoint, detailed data related to calculation of severity scores were collected for a random sample of both long- and short-stay patients, and prevalence surveys at the ICU-level were designed to estimate process and compliance measures.

We describe our approach for collecting data at different levels (e.g. patient, staff, and ICU), on a variety of schedules, and with different sampling schemes, address considerations and complications for creating analysis datasets from the different data structures, and report on the results of these techniques for capturing a wide variety of data with limited resources.

**P 70**

**MEASUREMENT ISSUES IN THE STAR*ICU CLUSTER RANDOMIZED TRIAL**

Charmaine M. Huckabee, W. Charles Huskins and Dennis D. Wallace
Rho, Inc., Chapel Hill, North Carolina, USA

Development of inhibitory antibodies (inhibitors) to replacement concentrates is the most severe complication of hemophilia. The etiology of inhibitors is multifactorial, involving genetic and environmental factors. While prospective evaluation offers the best opportunity for identifying related factors, data from retrospective studies are also informative. The current investigation examined the completeness of data retrospectively collected for the international Hemophilia Inhibitor Genetics Study (HIGS). A secondary objective of HIGS is to identify environmental factors associated with increased risk of inhibitor development. Data from 111 subjects with severe hemophilia A (median age 9.6), including 28 brother pairs, were analyzed. Rates of unknown data were examined for variables related to characteristics of hemophilia, inhibitors, treatment, and hospitalizations. Percentages of unknown values were calculated by dividing the number of questions with unknown values by the number of questions that could have responses. For participants with a brother also enrolled, a Pearson correlation was calculated to determine the correlation of percentage of unknown data between brothers. Mixed models controlling for correlated data were fit to determine factors related to the percentage of missing data. A maximum of 77 variables were considered. The median proportion of unknown data was 9%, range 0% to 62%. Variables least likely to be unknown were those collected as part of regular hemophilia care, such as exact or estimated date of first factor VIII treatment, characteristics of inhibitors, and occurrence of hospitalizations. The highest proportions of unknowns were observed for queries about total days of replacement therapy associated with hospitalization (including convalescence). Rates of missing data increased with increasing age, but did not vary by geographic region, inhibitor status, or whether the participant had a brother with hemophilia in the study. These results will be useful in guiding other researchers in their selection of hemophilia-related variables for inclusion in retrospective data collection.
The first year of the Frequent Hemodialysis Network (FHN) Trial Group’s nocturnal study (starting June 2006) was designated a Vanguard Phase during which feasibility of randomization, home training, and adherence could be evaluated. Four months into this Vanguard, investigators realized recruitment goals would not be reached under a design randomizing patients to three times/week in-center hemodialysis vs. six times/week home nocturnal hemodialysis. Few patients were willing to have a 50% chance of being randomized to three times/week in-center hemodialysis. The protocol was changed and patients are now randomized to three times a week home hemodialysis during waking hours vs. six times a week home nocturnal hemodialysis. This is advantageous in that all patients now undergo home training before randomization; under the previous design, a patient could be randomized to nocturnal hemodialysis and never receive it because he could not complete post-randomization home training. During the transition between the old and new protocols, patient measurements were suspended for about six weeks as clinical centers worked closely with their IRB’s to obtain approval for the new protocol and revised consent forms for 1) new patients, 2) patients in the baseline phase of the old protocol, and 3) patients who had been randomized under the old protocol. All recruitment, publicity, and patient education materials required revision. Distributed data entry screens and the study’s on-line randomization system needed to change quickly. The DSMB agreed that a new 12-month Vanguard Phase would begin when the first patient is randomized under the new protocol (anticipated January 2007). If the new Vanguard goals are met, 250 U.S. and Canadian patients will be randomized over a total of 26 months.

The FHN Core Cardiac MRI center and Quality of Life interview center provide standardized, blinded assessments of the study’s co-primary outcomes based on MRI and SF-36. The NIH and Centers for Medicare and Medicaid Services co-sponsor the study; cost effectiveness analyses are planned.

The PCPT was a randomized double blind chemoprevention trial designed to test the difference in the histologically-proven prostate cancer prevalence between a group of participants given finasteride and another given placebo for seven years. At the end of seven years, all men were to have an end-of-study biopsy to determine the presence or absence of prostate cancer. Between 1993 and 1997, 18,882 men were randomized. The primary analysis of the data showed a 24.8% reduction in the number of prostate cancers in the finasteride group vs. placebo (18.4% vs. 24.4%). However, there were an increased number of high grade prostate cancers on finasteride vs. placebo (6.4% vs. 5.1%). Yearly serum samples were collected and stored. There was an additional blood draw for the collection of white blood cells. Prostate tissue is available for the men from whom we have a prostate cancer diagnosis and for men who were determined to be cancer-free based on the end-of-study biopsy. These biologic specimens comprise a unique resource.

A program project (P01) with five inter-related projects is currently underway. The theme of the P01 is the genetic, metabolic and environmental factors associated with the risks of overall and high grade prostate cancer and the efficacy of finasteride as a cancer preventive agent. The statistical center for the PCPT is the Biostatistics Core for the P01. Each project has serum assays and genetic markers studies. At the conclusion, the Biostatistics Core will be responsible for developing a cross-project statistical model to look at the complex joint effects on prostate cancer risk. The development of the P01 including the choice of projects, study design, management of sample repositories and the overall coordination will be presented.

P 73
DATA CAPTURE BY DIGITAL PEN IN CLINICAL TRIALS: A QUALITATIVE AND QUANTITATIVE STUDY
Candice Estellat
INSERM, Hôpital Bichat, Université Paris, Paris, France

Objectives
To investigate the use and assess the accuracy of the digital pen (DP) system to collect data in a clinical trial.
Design Qualitative study based on semistructured interviews and a focus group. Quantitative study comparing the DP system and a double manual data entry system in accuracy of acquiring data.

http://ctj.sagepub.com
Abstracts

Setting An ongoing randomised multicentric clinical trial in tertiary care in France. Participants. 27 investigators who did or did not include patients, 4 study monitors and the study coordinator.

Results Six key findings emerged: 1) the DP system was almost as easy to use as a classical pen-and-paper case report form, even for investigators inexperienced in informatics; 2) despite its portability, the DP was not always used in front of patients; 3) the DP system did not affect patient recruitment; 4) most of the technical problems of the system occurred during setup (password access, antivirus software); 5) the main advantage was quickness of data availability for the study coordination staff and the main hindrance was the extra time required for online verification; and 6) all investigators were ready to use the system again.

The error rates for the DP and double manual data-entry systems did not differ significantly: 0.16% versus 0.12%; p = 0.79 (n = 5022 data entries). Most of the DP-system failures were due to the intelligent character recognition system.

Conclusion The DP system has a good acceptability among all investigators whether they are experienced with computers or not, and a good accuracy, as compared with double manual data entry.

P 74
ADHERENCE TO THE CONSORT STATEMENT IN EARLY BREAST CANCER (EBC) RANDOMIZED CONTROLLED TRIALS (RCTS) IN SYSTEMIC TREATMENT: A SYSTEMATIC REVIEW
Clare Peckitt
Institute of Cancer Research, Sutton, Surrey, UK

Introduction In 1996 the CONSORT (Consolidated Standards of Reporting Trials) statement was developed to improve manuscript quality. A systematic review, of all RCTs of systemic treatment in EBC published 2003–2004, was undertaken to establish extent and adherence to the CONSORT statement.

Methods Pubmed, Embase, Cochrane controlled trials register and references in identified articles were searched for keywords ‘Breast Cancer’ and ‘Randomized Controlled Trial’ published 2003–2004 in English. EBC was defined as ‘early’, stage T1–3, N0–1, M0 or ‘operable’. Systemic treatment included chemo-therapy, hormonal, immune or anti-angiogenesis therapies. Primary endpoint was time to an event. A global CONSORT adherence score, the number of points the publication adhered to (extracted independently by 2 reviewers), was used to determine quality. A score of 18 + (>=80%) was classed as good adherence.

Results 47 (10%) of 461 articles found met the entry criteria. Reasons for exclusion: advanced disease, not systemic treatment, not RCT. Only 14 (30%) trials were classed as good CONSORT adherers. Sections with 90% adherence were background information, intervention details, objectives/hypothesis, statistical methods, baseline data, interpretation and placing results in context of current evidence. Areas with high failure rates; 29 (62%) did not report fully on sample size justification; 28 (60%) reported only 1/3 of required randomization information; 34 (72%) did not include recommended CONSORT flow diagram; 22 (47%) did not fully generalize trials findings.

Conclusion Despite the CONSORT statement, publications of EBC RCTs still need improvement. Concentration on reporting of randomization procedures, sample size calculations, patients flow and generalizing trials findings could enhance greatly quality, interpretation and credibility of RCT articles.

P 75
ICEBERGS: A NEW SET OF CLINICAL TRIAL SIMULATION TOOLS
Eduardo Bergel
Instituto de Efectividad Clinica y Sanitaria, Buenos Aires, Argentina

To assist teaching, design, execution, and interpretation of randomized trials (especially when they generate unanticipated results) we have developed ICEBERGS, an innovative set of clinical trial simulation tools. Employing Monte Carlo methods and operating on personal computers, ICEBERGS simulates several thousand trials in a few seconds. Friendly menus (in English) permit users to specify baseline risks and responsiveness of up to four groups of trial participants (linking seamlessly to a sample-size calculator for both individual and cluster randomization). For each group, users can not only specify rates of cross-over, non-compliance, and lost-to-follow up, but also specify how these protocol deviations are to be managed in the analysis. Simulated results are displayed in both tables and figures. The former include overall relative risk (RR), relative risk reduction (RRR), their 95% confidence intervals, 2-tailed P-values, and power. The latter display histograms and dot plots of RR and RRR and scatter plots of their relation to P-values. All displays present both bias-free results and those resulting from protocol deviations and how they are managed in the analysis. Users also can apply Peto, Pocock, O’Brien-Fleming, or tailor-made stopping rules to their trials, specifying up to 5 interim analyses based on patient accrual and/or the number of events so far reported. ICEBERGS then reports the % of trials stopped early, the distributions of their results, and the extent to which the original estimates of RR and RRR were distorted due to early stopping. Use of ICEBERGS to date has enlightened not only less-numerate learners but also seasoned trialists (the latter often surprised by counterintuitive simulation results). ICEBERGS is available at no charge for attendees to this meeting at www.randomization.org.
TRIALS AND THEIR TRIBULATIONS: THE IMPORTANCE OF REALITY CHECKS WHEN PLANNING A CLINICAL TRIAL
Amy Kendrick Tracy Nolen Louise Zimmer and Dennis Wallace
Rho Federal Systems Division, Inc., Chapel Hill, North Carolina, USA

When planning a clinical trial, it is important to take into account the inevitable changes occurring in clinical practice. Clinical practice changes are to be expected as our knowledge increases and as cost-containment strategies become increasingly important in the organization and delivery of health care. Failing to recognize these changes and account for them within the protocol while it is still under development, can result in a protocol that is immediately outdated. Research resources then have to be expended on expensive and time-consuming protocol amendments. This situation can delay study enrollment, which can ultimately cause the research to become unfeasible (based on time and budgetary constraints). The discordance between a proposed protocol for multicenter research and current clinical practice has been encountered while carrying out several infectious disease protocols. Numerous issues arose that, if anticipated, could have either been avoided or addressed appropriately in the protocol specifications. Examples of issues encountered include: overly optimistic enrollment estimates, increased difficulty in obtaining informed consents, caregiver reluctance to adhere to protocols (when changes in current practice make protocol procedures outdated or conflict with the caregiver’s current practice), unexpected transfers and discharges of subjects in response to bed or staff shortages, and study entry criteria requiring procedures that are no longer routinely performed. Based on these experiences, we have developed guidelines to keep changes in clinical practice an integral part of the ongoing planning for any research trial.

DESIGNED EXTENSION OF SURVIVAL STUDIES: APPLICATIONS TO CLINICAL TRIALS WITH UNRECOGNIZED HETEROGENEITY
Yi Li Mei-Chiung and Shih Rebecca Betensky
Stanford University, Stanford, California, USA

It is well known that unrecognized heterogeneity among patients, such as is conferred by genetic subtype, can undermine the power of a randomized trial, designed under the assumption of homogeneity, to detect a truly beneficial treatment. We consider the conditional power approach to allow for recovery of power under unexplained heterogeneity. While Proschan and Hunsberger (1995) confined the application of conditional power design to normally distributed observations, we consider more general and difficult settings in which the data are in the framework of continuous time and are subject to censoring. In particular, we derive a procedure appropriate for the analysis of the weighted log rank test under the assumption of a proportional hazards frailty model. The proposed method is illustrated through application to a brain tumor trial.

EXPERTISE-BASED RANDOMIZED CONTROLLED TRIALS TO ASSESS SPINAL MANIPULATION AND ACUPUNCTURE FOR LOW BACK PAIN. A REVIEW OF RANDOMIZATION METHODS.
Bradley C. Johnston1, Bruno da Costa1, Jason Busse2, Elie Akl3, Jean-Jacques Dugoua4, Edward Mills2, and Philip Devereaux2,
1University of Alberta, Edmonton, Alberta, Canada
2McMaster University, Hamilton, Ontario, Canada
3University of New York, Buffalo, New York, USA
4University of Toronto, Toronto, Ontario, Canada

Background The randomized controlled trials (RCTs) has become the ‘gold standard’ for evaluating the efficacy of clinical interventions. Patients are typically randomized according to intervention; however, when treatment is influenced by the skill-set of the provider it is advisable to randomize patients to therapists skilled in the procedures under evaluation. This is known as an expertise-based RCT.

Objectives 1) To determine the number of RCTs that have compared the efficacy of different forms of SMT or acupuncture for low back pain (LBP) and have used an expertise-based RCT design; 2) To extract the parameters around the characteristics of these trials.

Methods A comprehensive search of six relevant electronic databases (e.g. EMBASE, MEDLINE) from inception to December 2005, and a grey literature search (e.g. reference lists, experts in the field) was conducted. Only trials of LBP that randomized participants to clinicians with expertise in A, or clinicians with expertise in intervention B, in where clinicians performed only the intervention they are expert in were included.

Results One hundred and sixty-seven RCTs of acupuncture or spinal manipulation for LBP were identified, with 17 exploring the effect of competing techniques; however, none of these trials used an expertise-based design.

Conclusions Trialists are not currently making use of expertise-based RCT design to evaluate acupuncture and spinal manipulation for LBP. This design offers a methodological safeguard against bias, referred to as “differential-expertise bias”, when undertaking the design of studies to explore the relative efficacy of competing therapies that are likely to be influenced by clinician’s skills.
WHAT IS THE MINIMUM CLINICALLY IMPORTANT DIFFERENCE (MCID) REQUIRED TO INTRODUCE A NEW TREATMENT INTO OBSTETRICAL PRACTICE? SURVEY OF CANADIAN OBSTETRICIANS

Jill Milne, Shannon Dwinnell, Cheryl Swaby, Stephen Wood and Sue Ross
University of Calgary, Calgary, Alberta, Canada

Sample sizes for obstetrical trials are often based on the opinions of investigators about the size of effect that is clinically important. We surveyed Canadian obstetricians to investigate the MCID required before they would introduce treatments to prevent preterm birth.

Method Forced choice questionnaires were mailed to 1293 practising obstetricians, asking what increase in length of gestation would be required to introduce treatments into their clinical practice to prevent preterm birth. The three prophylactic treatments were of increasing invasiveness: vaginal (PV) progesterone, intramuscular (IM) progesterone, and cervical cerclage.

Results 537 (41.5%) completed questionnaires were received. Two weeks was the most frequently endorsed MCID to introduce progesterone PV for women with multiple gestations (202, 39.9%), and progesterone IM for women with singleton pregnancies and risk factors for preterm birth (208, 41.3%). Three weeks was required before introducing prophylactic cerclage for women with a short cervix (316, 62.9%). Wilcoxon tests found that a larger difference was needed to introduce progesterone IM than progesterone PV (p = 0.004), and a larger difference to introduce cerclage, compared to progesterone PV (p = 0.000) or IM (p = 0.000). Clinicians who already used a treatment would require a smaller difference before introducing that treatment prophylactically. Although an increase in length of gestation would be sufficient to change practice, clinicians stated that decreasing neonatal morbidity was the most important outcome for obstetrical trials.

Discussion We found that more invasive treatments required a larger MCID before clinicians would introduce them into practice. The nature of the treatment, the proposed outcome measure and clinicians’ current clinical practice all impact on MCID.

A PROCESS FOR THE DEVELOPMENT OF INVESTIGATOR INITIATED TRIALS IN KIDNEY DISEASE IN AUSTRALIA AND NEW ZEALAND

Daniel P. Francis, Elaine Beller, Carmel Hawley and Brenda Rosser
University of Queensland, Queensland, Australia

Background The Australasian Kidney Trials Network (AKTN) was established to help improve the capacity to conduct investigator initiated clinical trials in kidney disease in Australia and New Zealand. The network has implemented a process to guide the development of trials from original concepts to full trial protocols.

Methods Clinicians from throughout Australasia are able to submit brief synopses of trial concepts to the AKTN. These are appraised by the secretariat (which provides the bio-statistical and data management expertise and infrastructure of the network) before being reviewed by two members of the scientific committee. It is the responsibility of the scientific committee to provide advice on the clinical importance, feasibility and design issues of the trial, and to work with the proposer to develop these aspects of the study. Using the recommendations provided, the proposer may then further develop the trial before it is voted on by the entire scientific committee. Upon approval, a trial management committee chaired by the proposer, and including the scientific reviewers and biostatistician is formed. This group is charged with developing the protocol further, encouraging collaboration, and facilitating funding requests. Once the protocol is completed it is then re-submitted to the scientific committee for final ratification.

Results Three trials have now been developed into full protocols using this process. One of these has received funding from the National Health and Medical Research Council (NHMRC) of Australia. Collaboration has been sought from the wider nephrological community of Australia and New Zealand and each trial is now expected to commence in 2007.

Conclusion This process of trial development implemented by the AKTN has been successful in developing high quality, clinically important, and feasible investigator initiated clinical research in kidney disease in Australia and New Zealand.

ON THE ROAD TO PERSONALIZED MEDICINE: PHARMACOGENETIC TESTING IN CLINICAL TRIALS

Jawahar Tiwari, Dale Horne, Ghanshyam Gupta and Raj Puri
U.S. Food & Drug Administration, Rockville, Maryland, USA

Pharmacogenetic Testing for evaluation of associations between genes and drug response will enter clinical trials during Phase 2 and 3 studies. Such studies, when performed for drug licensure, are designed with randomization, a set of prespecified primary and secondary endpoints, an alpha level of 5%, and a power of 80 to 90% for testing the hypothesis with respect to the primary endpoint of efficacy.
In this setting, genetic association analysis will be a secondary objective of the trial. The analyses of genetic associations with drug response (clinical measurements of efficacy and/or safety) will utilize only the cohort of patients randomized to the drug-treated arm of the trial. Thus, in a two-arm trial, the available sample size for analysis would be reduced by half. A simple analysis of association can be performed with the use of a $\chi^2$ test applied to a $2 \times 2$ contingency table in which patients are divided into “responder,” “non-responder,” single nucleotide polymorphism (SNP) positive, and SNP negative categories. The corresponding sample size for evaluating genetic association will depend on the frequency of the gene in the responders and non-responders. In an ethnically diverse patient population, the candidate gene frequencies may differ by ethnicity. In this research we evaluate and compare the sample size requirement under various genetic models of inheritance (dominant, recessive, and additive) for a genetic association study embedded in a randomized trial.

Since analysis of genetic associations with drug response will utilize only patients from the drug-treated arm of the trial, it is important to match responders and non-responders with respect to their genetic background. Presence of population stratification and/or genetic admixture may produce false positive results.

### P 82

**DEVELOPING AN AUDIO COMPUTER-ASSISTED SELF-INTERVIEWING SYSTEM FOR HANDHELD COMPUTING DEVICES**

Stephen D. Litavecz, Norman Goco and Kevin Wilson
RTI International, Inc., Research Triangle Park, North Carolina, USA

For improved data quality, mobility, and cost-effectiveness, RTI has developed an audio computer-assisted self-interviewing (ACASI) system for handheld computing devices, a technology that allows questionnaires to be self-administered. Respondents view questions and responses on the screen while listening as each are read. Headphones are used to ensure confidentiality. The system uses prerecorded sound (WAV) files for the audio component. The respondent selects a response using a touch screen. When a response is selected, it is highlighted and read again so that data are recorded accurately. ACASI technology is especially effective in collecting sensitive respondent data (e.g. drug use, sexual practices, etc.) and with low-literacy respondents.

The system offers the ability to administer questionnaires in multiple languages and provides skip logic, numeric range checks, and date checking. Standard question types include:

- Information screen
- Radio
- Checkbox
- Numeric entry from onscreen keypad
- Text entry with virtual keyboard

In addition, the system offers new methods of data capture including the ability to record spoken responses and collection of participants’ signatures, allowing for verification of informed consent. The system is well-suited for global clinical trials due to its support of multiple languages, data quality, and mobility.

The system is expected to save project resources by requiring fewer interviewers to conduct group surveys and decreasing time required for setup. Response rates may be improved because of the decreased burden on participants, while response accuracy may increase due to the system's error checking during data entry and protection of participants' privacy. Handheld devices can be carried inconspicuously, which makes them a viable alternative where security is a concern. Handhelds are less costly and offer features comparable to laptop computers.

### P 83

**A SYSTEM FOR RAPID DATA EDITING OF WEB-ENTERED DATA IN A CLUSTER DESIGN TRIAL**

Preethy M. Kolinjivadi, Daniel Miller and Laure El ghormli
The George Washington University, Rockville, Maryland, USA

The HEALTHY study is a 3-year cluster design trial involving 42 middle schools at 7 field centers nationwide. Baseline data collection on over 6000 sixth grade students took place over a compressed time period during the first 4-months of the 2006–2007 school year. Data collection includes a health screening (height, weight, waist, blood pressure) and fasting blood draw. Field center staff enter data into a web-based system and send blood samples to a central blood laboratory (CBL). The families of participating students receive personalized letters reporting measurements. The coordinating center needs to provide quick turnaround in processing data and returning it to the field centers for the feedback letters. The coordinating center implemented a streamlined process of data editing for quality control.

This process is as follows:
1. Field center notifies the coordinating center when data entry for a school is complete.
2. Coordinating center staff creates an edit report using SAS. The report includes missing values, discrepancies, and faulty skip patterns.
3. Coordinating center staff send an additional report of data outliers to the field center principal investigator and to the study physician for review and confirmation or resolution.

http://ctj.sagepub.com
4. The field center staff make all necessary corrections to the database using the web.
5. After all queries are resolved, coordinating center staff create an Excel file with cleaned health screening data merged with CBL results.
6. Field center staff mail-merge these data along with locally maintained student identification data into student-specific results letters.

The data editing process for each school is generally completed within a week. We find this process to be efficient in coordinating data editing that permits rapid turnaround.

P 84
DATA MANAGEMENT IN ELECTRONIC DATA COLLECTION SYSTEMS
Gladys C. McPherson, Alison McDonald and John Norrie
University of Aberdeen, Aberdeen, UK

With the increasing use of electronic data collection (EDC) is there still a role for the data manager in clinical trials? Recent publications have posed the question ‘Has technology eliminated the need for a data manager or has the nature of the work just changed?’ The data manager is responsible for tasks that ensure data is accurate, compliant, timely and accessible. The role of the data manager traditionally includes database administration, storage, backup, security, quality assurance, reporting and often analysis. Data validity and integrity can be managed by checking values either on the data entry system (such as Web forms) or within the database itself. However, the system must not be too stringent so as to prevent data entry. Missing values and anomalies may be flagged later by a separate piece of programming which issues reports at regular intervals.

With the shift towards EDC the data manager role may utilise more electronic and often automatic solutions to data quality tasks. Pre-specified rules and constraints may be logged in a separate database and this can be used to generate queries automatically. It may be possible to build up a library of data solutions so that the data manager is not employed on a per study basis but rather can operate more efficiently across several studies with the same set of tools. The skills needed to develop and maintain such a generic system are highly specialized and perhaps do indicate a change in the nature of the work undertaken by the data manager. However, no-one is better placed to make these changes than the data managers themselves.

1. Applied Clinical Trials Volume15, Number10 October 2006.

P 85
DATA MANAGEMENT TOOLS IN THE DOMINO TRIAL: DHA IN PREGNANCY TO PREVENT POSTNATAL DEPRESSIVE SYMPTOMS AND ENHANCE NEURODEVELOPMENT IN CHILDREN:
Philip Ryan, Elizabeth Griffith, Brian McDermott, Maria Makrides and Robert Gibson on behalf of the DOMInO Steering Group
University of Adelaide, Adelaide, South Australia

The DOMInO study is a national, multicentre, double blind trial of fish oil capsules, rich in docosohexaenoic acid (DHA), versus placebo in pregnant women from 20 weeks gestation until birth. The Edinburgh Post-Natal Depression Scale (EPNDS) will be administered to 2200 women at 6 weeks and at 6 months post-partum. In addition, all preterm infants and a random sample of term infants (n = 750 approx) will be assessed at 18 months using the Bayley Scales of Infant Development. DOMInO is the most comprehensive study to date on the effects of fish oil supplementation on the well being of mothers and development of infants.

We present the data management plan for this study and demonstrate some of the tools we have developed to support it. In particular we discuss integrated support for substudies, notification processes for subjects considered at-risk on the basis of the EPNDS, and a sophisticated query raising and resolving tool.

P 86
CONVERTING TO THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES (MEDDRA)
Eric A. Krum, Ray Nelson and Greg Thompson
University of Minnesota, Minneapolis, Minnesota, USA

Accurate, consistent coding and classification of clinical data is essential for ensuring the validity of clinical trial results. To this end, regulatory authorities and the biopharmaceutical industry have developed MedDRA, the standard for coding of medical information in clinical research. We describe the experience of our statistical and data management center in converting from ICD-9CM to MedDRA for the coding of adverse event data collected in HIV studies.

MedDRA conversion was carried out under the direction of a consultant appointed by our sponsor. The following steps were necessary to complete the conversion:
• Training of coders, IT, and statisticians on the fundamentals of MedDRA
Developing an overall implementation plan
Converting legacy data
Establishing the database
Identifying and developing or modifying standard operating procedures and policies to support MedDRA-related activities
Developing a coding tool to support term selection
Identifying training needs and developing training for clinical trial sites
Planning for version control

This poster will further describe the steps in our conversion process, what we learned, what went well, potential pitfalls, and advice for others.

P 87
THE DESIGN AND IMPLEMENTATION OF A CENTRALIZED CONTACTS DATABASE FOR COORDINATING SEVERAL MULTICENTRE RCTS
Sunny Chan, Michael Shi, Cathy Yang, Anthony Armson and Sheila Hewson
University of Toronto, Toronto, Ontario, Canada

The University of Toronto Maternal, Infant and Reproductive Health Research Unit (MIRU) is the data coordinating centre and administrative site for several international RCTs. The Trial Coordinators and Research Assistants (RAs) at MIRU communicate with investigators and coordinators at numerous centres on a regular basis. It is essential that accurate contact information is recorded in a database as it is used frequently to send trial newsletters, start-up packages, contact reminders, overdue data reminders, funding payments, and other trial information. Previously, contact information for our collaborators (investigators, co-ordinators, and other clinicians) was stored in separate databases according to their involvement in a specific trial and the task of updating information would be the responsibility of the Trial Coordinators and RAs. We have found that the process of updating contact information is often time consuming and error-prone when synchronizing records contained in several databases. Therefore, we decided to design a centralized database to store the essential contact information. One of the main advantages is that Trial Coordinators and RAs are able to access contact information specific to their trial as well as other MIRU trials. Furthermore, they could add, remove, and update contacts easily from one location. In future, the database could be expanded to allow users to access from a web-browser and also to add the capability of tracking user changes using the auditing feature. After completion, the database would be a valuable resource for coordinating multicentre RCTs with the added benefit of easier data management.

P 88
CREATING A NETWORK-WIDE REGISTRY: THE CORE DATA PROJECT OF THE COLLABORATIVE PEDIATRIC CRITICAL CARE RESEARCH NETWORK
Amy Donaldson1, Jamie Bell1 and Michael Dean1 for the NICHD Collaborative Pediatric Critical Care Research Network
1University of Utah, Salt Lake City, Utah, USA
2National Institutes of Health, Bethesda, Maryland, USA

The Collaborative Pediatric Critical Care Research Network (CPCCRN) was established in 2005 by the National Institute of Child Health and Human Development and consists of six clinical sites and the Data Coordinating Center (DCC). The CPCCRN Core Data Project collects information on all PICU discharges from existing electronic databases at each site annually. These data are used in planning clinical trials. There are a total of 17 data elements collected including patient diagnoses, procedures, and disposition. Data are submitted via a secure web-based collaborative workspace. Site-specific formats and values are transformed as needed to match the master database. Detailed reports of the data are generated and reviewed by both the DCC and site investigators for accuracy and completeness. Once the data are finalized for all sites, the information is published via a series of online analytical processing (OLAP) cubes. The OLAP cubes enable the end user to cross tabulate the database in an intuitive manner. Reports can be accessed interactively, i.e., built by an individual user, or predefined so that all users have access to the same information. Users can access cubes via the Internet using a web browser that supports https access (encrypted connection). Individual user accounts and password authentication is required. In multi-center research networks, a registry describing the basic characteristics of the patient population can provide the data necessary for hypothesis generation, study design, preliminary power analyses, and recruitment projections. We describe the process to collect these data and provide network investigators with secure and flexible access to the information.
Today's complex clinical research projects require sophisticated information systems to properly support study and data management. As the complexity of these systems rise, so does the chance that some portion or component of the system will fail to operate as expected, requiring additional efforts to identify and correct the problem, and to subsequently identify and clean any data that may have been affected. These complex systems, and the data they support, could benefit greatly from the implementation of standardized development practices. This process begins with establishing standard processes that will govern how systems are built, tested, implemented and maintained. It involves understanding user requirements, developing and implementing standardized application development, and having proper change control process in place to manage maintenance efforts, and much more.

But developing and implementing these practices is not a simple task. In a multi-developer environment, getting consensus on what best practices are, and which standards should be implemented, and the best mechanism to manage that implementation, can make this process even more challenging.

In this presentation, we will discuss how one group is trying to overcome these challenges and by implementing standardized development practices, with the goal of improving the quality of both the systems used in clinical research projects and the quality of the data being collected.

Data management within a clinical trial setting has become an increasingly critical task. Technology has given us additional flexibility with how we gather and analyze data while government regulations such as HIPPA and the FDA's 21 CFR Part 11 mandate the protection and privacy of the data we collect. Protecting the integrity and privacy of the data becomes more complicated when you have multiple data users accessing the data in a variety of ways. Protecting data in a multi-tiered environment means enforcing security measures at every network tier, from the internet to the individual client, and applying safeguards for all servers and software which are involved with the capturing and analyzing of study data.

SQL Server is used as a central collection point for data. Access to the data is controlled by SQL Server's security protocols and is determined by departmental and study directives. Statistical and study specific data sets are safeguarded against non-authorized activity.

Additional security measures are incorporated into the client interface as well. These include custom error handling to prevent divulging system-specific information, logging of all user activity within the system, logging of all attempts to gain access to the system and validation of inputted data.

Physical security is also an important factor in the overall project security plan. Housing critical hardware in a secure area and ensuring workstations are locked and password protected when not in use are just a few of the methods typically used in physical security plans.

The requirements for data protection and privacy are challenging in today’s complicated studies. In this presentation, we will demonstrate how one project manages these tasks while conforming to government regulations.

As the volume of information processed by Institutional Review Boards continues to grow, the demand for a paperless solution is greater than ever. Though electronic application submission is a positive start, it is only the first step to a full scale automated process that encompasses the tools necessary to conduct 100% paperless review, approval and post approval activities for IRB applications. In 2004 Wake Forest University Health Sciences selected a base extranet product and developed eIRB, a fully web-based submission system that in less than one year has revolutionized its IRB submission and review process.

Ancillary committee approval is built into the system to enhance compliance at the institutional level; error checking and document versioning keep data current and correct; email notifications and inbox functionality keep projects moving, and routing time is reduced to zero. The roles of the IRB staff have changed dramatically allowing for a more thorough pre-review of applications resulting in a comprehensive review by Board members and faster turn-around time for approvals.

Clinical Trials 2007; 4: 371–455  http://ctj.sagepub.com
Lessons learned during implementation highlight the need for strong network and server management infrastructure, dedicated programming support, vendor availability and commitment and focused effort from the IRB staff in defining business rules. Beyond implementation, new challenges of paper study conversions and modifications to workflow processes have underscored the need for the solution to be highly flexible. Since October 2005, over 700 new applications have been initiated in eIRB with an additional 175 paper conversion projects. In this period of time, over 900 distinct users have logged onto the system to participate in the processes automated by the application. In 2005 WFUHS joined a consortium of institutions to share and innovate new practices that have broad-based practical applications for research regulatory process automation.

P 92
PHASED TRANSITION FROM TRADITIONAL DATA ENTRY TO A WEB-BASED SYSTEM
Joel Achtenberg, Karen Clark, Mary Bednarski, Elizabeth Hornbeck, Mae O. Gordon and The Ocular Hypertension Treatment Study Group
Washington University School of Medicine, St Louis, Missouri, USA

When converting from traditional, centralized data entry and management to a distributed web-based system for an on-going multi-center clinical trial, it was impractical to attempt converting all of our form types at once; rather, we adopted a phased transition strategy in which new forms and features were brought on line in stages while the original “legacy” system continued to function normally.

The Ocular Hypertension Treatment Study (OHTS), which began in 1994, has 38 participating clinics, 1636 patients, 32 clinical and administrative forms. All data, in both the legacy and web-based systems, are stored in SAS data libraries, although the structure and organization of the data is different on the two systems. Because data for each form type could be entered and updated in only one system at a time, this phased approach has required careful attention to the timing of each move, effective communication with users, and rigid procedures for locking, converting and unlocking of datasets.

Transition to a web-based system began in September 2004, and continues to date. Through November 2006, thirteen form types, including all major forms currently in use, have been successfully converted to web data entry. We provide rationale for the sequence of implementation, and describe unanticipated problems, advantages and disadvantages of a phased approach for implementing a web-based system.

Support: Grants EY09307 and EY 09341 from the National Eye Institute and the National Center on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD; Merck Research Laboratories, White House Station, NJ; and by an unrestricted grant from Research to Prevent Blindness, Inc, New York, NY.

P 93
WEB-BASED STUDY ARCHIVE AS A TOOL FOR STUDY ANALYSIS
Elizabeth Hornbeck, Joel Achtenberg, Mae O. Gordon and The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group, Washington University School of Medicine, St. Louis, Missouri, USA

The CLEK study is a multi-center (16 centers) observational study to characterize the prognosis of keratoconus patients. CLEK participants (n = 1,209) completed comprehensive eye examinations at enrollment and annually thereafter for eight years. The study closed in 2004.

A study archive website https://vrcc.wustl.edu/clekarchive was developed to support a wide range of users including study investigators, members of the scientific community at large, patients with keratoconus, and the general public. One unique and heavily used feature is the conversion of study case report forms (CRF) to interactive, annotated PDF forms using Adobe Acrobat Professional. Using form fields, each study variable is annotated on the CRF and linked to details from the dataset. The information is then presented in html format. This feature allows users to quickly view variable-specific information within the datasets i.e., exact wording of questions and response options thereby preventing errors in variable selection and interpretation. This feature has become an invaluable tool for support of writing committees, statisticians and programmers.

Grant Support: EY10419, EY10069, EY10077, EY12656, EY02687, Conform Contact Research Foundation, and unrestricted grants from Research to Prevent Blindness.

P 94
Heather Sampson, Phyllis Bettello, Melanie Walker, Tammy DeGelder, Lisa Lewis, Tanis Coletti, Judith-Elise Marcoux, Linda Illes and Janice DeWit
Toronto East General Hospital, Toronto, Ontario, Canada

Background Presently no standardized education tool or program exists to manage knowledge transfer (KT) of clinical trial research ethics and regulatory changes in Canada. Geographic and demographic disparity present
challenges to communicating changes to the NCIC CTG membership. This report describes the experience of introducing and evaluating an education update presented at the NCIC CTG annual meeting of participants over the last four years, based on ongoing needs assessments, program implementation and evaluation. Since 1971, NCIC CTG has enrolled more than 53,000 patients in over 300 clinical trials. Over 3000 Canadian physicians, research nurses, data managers and pharmacists participate in the local administration of these trials.

**Methods** Based on annual membership needs assessments the NCIC CTG Ethics and Regulatory committee designs and implements annual educational updates. Attendees completed 108 evaluation surveys for the 2006 session. Qualitative/quantitative evaluation was performed.

**Results** Due to room/volunteer restrictions attendance is limited; two sessions are run with maximum attendance. Survey/assessment in the 108 completed surveys/assessments demonstrated that 64 respondents had >3 years experience. Additional data results will be presented.

**Conclusion** This KT technique demonstrates effective cross-country communication that will facilitate the continuation and further development of NCIC CTG national ethics and regulatory education. The data indicate that the face-to-face annual meeting program delivers effective education; the need for further standardization and improved education exists.

**Recommendation** To insure national inclusion for research ethics and regulatory education standardization this program should continue plus introduction of web-based e-learning tools, to be developed and tested to better serve membership unable to attend the annual meeting/education update.

---

**P 95**

CREATING AND IMPLEMENTING A WEB-BASED RESEARCH ETHICS REVIEW TEMPLATE BASED ON IDENTIFIED VARIATIONS IN THE RESEARCH ETHICS BOARD (REB) REVIEW PROCESS: A CANADIAN MODEL

Heather A. Sampson, Joyce Nyhof-Young, James Brierley, Tony Panzarella, David Wiljer, Don Short, Ronald Heslegrave, Laura Nash, Alanna Salpeter, Kate Malisani, Katie Gouinlock and Ross Upshur

**Background** This report presents the Canadian Institutes of Health Research funded phase 2/3 study to assess the utility of a Canadian web-based REB protocol and consent review template. REB focus groups conducted in 2006 combined with Phase 1 data reporting on REB structure, activity and education indicated criteria that informed the creation, testing, piloting and implementation of the template at Canadian academic and community-based REBs.

**Methods & Results** Three focus groups were held with cross-country, academic/community REB representation (N = 20) with primary objectives to:

- discuss opinions, build consensus on the need for a standardized web-based protocol and consent review system;
- identify issues, concerns, and implications of a template: impact on REB functionality; REB-investigator relationships; patient-participant accrual and outcomes; clinical research; government policy; legal liability; and social factors;
- develop insight into how to build an easy-to-use and effective REB tool

Working with Infonetica (UK software developers) a web-based template was designed using focus group and phase 1 information. Introducing/piloting the template at 21 REBs entailed gaining trust and acceptance from chairs, members and coordinators. Implementing change/innovation necessitated face-to-face meetings, presentations and intense support in the early stages of implementation; however independence and self-management quickly followed. REBs have given valuable feedback for template edits and modifications. REB experiences and recommendations will be presented.

**Conclusion** These data demonstrate continued effective cross-Canada REB communication/collaboration for template development. The data indicate the desire for standardization and education as provided by this web-based tool; further distribution/refinements are ongoing.

---

**P 96**

IMPLEMENTING AND MAINTAINING CLINICAL TRIAL REGISTRIES

Gabriele Dreier, Rainer Peters, Martin Lucht, Sven Barten and Herbert Maier-Lenz

University Medical Center Freiburg, Freiburg, Germany

Medical development and continuous increase in knowledge in the field of clinical research require a rapid dissemination of information. Clinical trial registries are crucial to make information about planned, ongoing and finished trials publicly available. The member journals of the International Committee of Medical Journal Editors (ICMJE) require the registration of a clinical trial as a prerequisite for accepting a paper. Due to the global activity in clinical studies, the implementation of national, European or e.g. disease-specific registers should take place in close cooperation with international registers and the WHO’s International Clinical Trials Registry Platform (ICTRP).
We implemented two registers at the Centre of Clinical Trials (ZKS), a department of the University Medical Center Freiburg.

1. German Somatic Gene Transfer Clinical Trial Database (DeReG) The aim is the permanent implementation of a database containing all somatic gene transfer clinical trials conducted in Germany. DeReG was established in cooperation with the Commission of Gene Therapy of the German Medical Association and the German Society for Gene Therapy. DeReG is embedded in national and international register activities.

2. University Hospital Freiburg database of clinical trials (UKLreg) We were the first in Germany to register all clinical studies conducted at a university hospital. Supported by the Medical Faculty and the University Medical Center Freiburg, the registry is run in cooperation with the University hospital’s ethics committee.

Implementing clinical trial registers is a scientific rather than an administrative act and should be done by a multi-disciplinary team in close cooperation with ethics committees to achieve completeness. International cooperation is needed to harmonize register content, quality assurance, data management and data analysis and to facilitate data exchange.

P 97

SPONSORSHIP IN INVESTIGATOR INITIATED TRIALS – ALLOCATION OF RESPONSIBILITIES AT THE UNIVERSITY HOSPITAL OF HEIDELBERG, GERMANY

Steffen Luntz
Coordination Centre for Clinical Trials (KKS), Heidelberg, Germany

ICH-GCP defines a sponsor of a clinical trial as an individual, company, institution or organization which takes responsibility for the initiation, management, and/or financing. In the course of an amendment of the German Drug Law in 2004 ICH-GCP became legally binding in Germany. Clinical Trials not conducted by the pharmaceutical industry are mostly initiated by academic investigators working at a university hospital. The increasing requirements stipulated by international guidelines, directives, and laws make it difficult for these investigators to be aware of all their responsibilities as a sponsor. As clinical research belongs to the duties of academic clinicians, their employer, i.e. the university, is ultimately responsible for the adherence to all rules. The department for general administration has to define procedures which ensure the correct conduct of clinical trials on the one hand while maintaining an attractive research environment on the other.

Therefore, the Medical Faculty Heidelberg implemented a non-bureaucratic procedure. A checklist itemizes all regulatory tasks for clinical trials. The coordinating investigator has to check off which obligations he will fulfill himself and which will be delegated, e.g. notifications to competent authorities, safety aspects or clinical monitoring. After this list is signed by the investigator and by any other person assuming a specified responsibility it has to be included in the application to the Ethics Committee. The EC forwards it to the administrative department. This simple measure yields several benefits: investigators become aware of their regulatory obligations, the administration ascertains that all aspects are considered and responsibilities are assigned to named persons.

P 98

INTENT TO TREAT VS STRATIFIED RANDOMISATION AND SUBGROUP ANALYSIS – WHICH EVIDENCE IS SUPERIOR?

Joerg Hasford
University of Munich, Munich, Germany

The reimbursement of the costs of prescription drugs is influenced in many countries by national agencies which review the clinical and cost effectiveness of new drugs. This post hoc evaluation can generate very controversial results and may influence the design of future randomized trials. The German Institute for Quality and Efficiency in Health Care recently reviewed the CAPRIE trial (Lancet 1996;348:1329–39). CAPRIE was a large (n = 19185) placebo controlled trial.

Randomisation was stratified for three different medical histories, each qualifying for admission. Sample size estimation was performed aiming for an intent to treat analysis of all randomised patients irrespective of the strata. The final ITT analysis of the primary endpoint showed a statistically significant result (p < .05). The reviewers focused however on the results of subgroup analyses: As subgroup A showed its own significant difference and the corresponding test for interaction was significant too they concluded that proof of effectiveness had been shown for subgroup A only and not for all patients included in the ITT analysis. This type of reasoning raises important methodological issues like the validity of post hoc assessments vs trial protocol based prespecified ITT analysis; the need of adjusting alfa for multiple testing, and the design of clinical trials (e.g. stratified randomisation or not) which will be discussed. This experience stresses the need for accepted standards for the evaluation of the validity of subgroup analyses.

http://ctj.sagepub.com
Efficient communication and exchange of information between the coordinating and clinical centers are critical to the success of a multi-center clinical trial. Web-based PDF forms provide an excellent method for clinical center personnel to submit to and view data in a shared central database. Creating a Web-based form and the underlying database do not require special programming knowledge. For example, Adobe Acrobat Professional provides users with a friendly development environment to build active PDF forms and Microsoft Access makes it easy for a user to create a database. However, to implement the online data submission process, the user must write code to interact with the Web server using a standard tool such as ASP code. ASP and similar tools require programming skills, and the lack of these skills on the part of the user may prohibit the use of Web-based forms.

Using SAS®, the Epidemiology Data Center at the University of Pittsburgh has developed and implemented a method to automatically generate the files needed to connect to a central database and then enter or view data via active PDF forms. To facilitate the use of active PDF forms, a SAS program reads the structure of the database and generates specific data access routines (i.e. connect, submit, and view). When the generated code and the PDF form are transferred to a Web server, the online form is ready. Thus, the SAS program allows users without programming skills to implement an efficient data exchange tool that requires a high level of interaction between an active PDF form and a shared central database.

Despite the promise of web-based data capture as a means to reduce time and costs in the clinical trials process, it is not always feasible to use online data capture tools where the communication and Internet service are not reliable. As the data coordinating center (DCC) and administrative site for several international multi-center RCTs, the implementation of a system that can incorporate both paper-based and web-based data collecting methods into a unified data management process is required.

Verity TeleForm is a key component of this hybrid system, allowing the user to design a form once and publish it as paper, HTML or fillable PDF, eliminating the need to redesign the same form in multiple formats. The HTML or PDF forms can be posted on a website or distributed via email, giving end-users multiple options for completion. Hand-printed forms can be faxed or scanned into Verity TeleForm.

To ensure the security and integrity of the data, the secure sockets layer protocol is used to encrypt all exchanges between a user and the server in order to prevent tampering or data forgery. As a further safeguard, access to all data on the server is controlled by password protection and user/profile permissions. Data quality is maintained through restricted entry, client-side data validation and range checks.

The paper-web hybrid data capture system combines the familiarity of paper forms with the convenience of web-based applications. The initiative has the potential to help us seamlessly integrate online data capture with traditional paper-based processes, to improve the efficiency and cost-effectiveness for international multi-center RCTs.
created by pulling objects from the Shape Library to a template specific to the form. It also provides the possibility for the trial coordinator to work with the TELEform™ forms directly and skip the initial design in Word. In conclusion, our new approach improves and speeds up the process of data form design which allows us to start up the recruitment and send out TELEform™ forms at early stage for better data integrity and data quality.

P 102
DESIGNING AND MAINTAINING AN ORGANIZATIONAL WEBSITE FOR CLINICAL TRIAL REGISTRATION MANAGEMENT
David Garnand, Grant D. Huang and Mike R. Sather
VA Cooperative Studies Program, Albuquerque, New Mexico, USA

Clinical trials registration plays an important role in helping the public to be informed about research that may impact their lives. The U.S. Department of Veterans Affairs Cooperative Studies Program (CSP) specializes in designing and conducting multi-site clinical trials and epidemiological research on key diseases that impact our veterans and the nation. The CSP has a long-standing policy for registering its trials and has developed a web-based system to register and manage over 70 trials with Clinicaltrials.gov, a public Protocol Registration System (PRS) sponsored by the National Library of Medicine.

A web-based trials registration system needs to consider several elements in its development and architecture. These elements include: understanding minimal informational requirements; incorporating management efficiencies for new and on-going studies; querying capabilities, and field and form validation. Further, added capabilities may include referencing trial information from outside sources.

Such a system is described that collects data from eight national CSP centers. This system is based in part on World Health Organization minimum registration data set requirements and other technical elements. Additionally, challenges involved with developing this type of system are presented. Examples of these challenges include:
• Uploading trials as collection versus single trial upload
• Managing study status (not yet recruiting, recruiting, completed, etc.)
• Managing sites and contacts as they are added and their status
• Contacts- overall and site specific with backups
• Formatting issues (text fields, dates, etc.)
• Required fields and other form validation issues
• Using appropriate key words to aid in searching

Providing clinical trial information publicly effectively allows health care personnel to make informed decisions, as well as giving patients access to participate in the newest medical interventions.

P 103
MANAGING PHARMACEUTICAL DRUG SUPPLIES IN A CLINICAL TRIAL USING RADIO FREQUENCY IDENTIFICATION (RFID) TAGS
Jimmy Pontzer, Bryan Del Curto and Stuart Warren
VA Cooperative Studies Program, Albuquerque, New Mexico, USA

The Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC) supports a large, multi-center clinical trial which requires the tracking, packaging and distribution of close to thirty different drugs and ancillary supplies. Since the trial began in May 2000, the CRPCC has shipped over 265,000 items to 20 sites. Initial pharmaceutical handling procedures relied upon study-specific, bar-coded labels applied to the items, with each item being individually scanned using a hand-held barcode scanner and custom software written by CRPCC staff.

The CRPCC recently chose to implement radio frequency identification (RFID) tags in the study item labels in order to increase productivity, eliminating the need for individual items to be scanned. Barcodes and human-readable information on the labels would remain only as a back-up measure.

This presentation details the challenges and results of implementing RFID technology in an on-going clinical trial, including:
• The selection process for choosing an appropriate study to pilot the technology.
• The installation of specialized hardware, including RFID tag readers and antennae, in the CRPCC’s drug processing area.
• The modification of existing drug-handling processes to incorporate RFID technology.
• The writing of software applications in a specific language, C# .NET, in order to interface with the application programming interface (API) of the RFID hardware.
• The seamless integration of the new software with existing applications and databases which were written in dBase Plus.
• The documenting of improvement in processing time and the subsequent cost-benefit while maintaining current drug accountability standards.
P 104
COLLABORATIVE EFFORT TO FACILITATE LARGE DNA SAMPLE SHIPMENTS THE TYPE1 GENETICS CONSORTIUM (T1DGC)
Dustin T. Williams, June Pierce, Letitia Howard and Joan Hilner
Wake Forest University School of Medicine, Winston Salem, North Carolina, USA

Finding a balance between the need for accurate specimen tracking and overwhelming laboratory staff with data entry is an important issue. Even the most efficient laboratories struggle with logging thousands of samples. The T1DGC Coordinating Center (CoC) systems, statistics and operations teams collaborated to create cutting-edge shipping manifests to aid the four international DNA Repositories with frequent large sample shipments. By utilizing multiple programs the T1DGC CoC developed shipping manifests containing barcodes for every sample ID included in a shipment. The repositories confirm availability of all samples and the generated manifests permit laboratory staff to enter all sample IDs into the T1DGC specimen tracking system rapidly and efficiently, by scanning the barcodes on the manifest.

The creation of these manifests requires accessing multiple programs. SAS is used to determine the samples to be included in a given shipment and inserts the sample IDs into a SQL Server database table. SQL Server is utilized to store the shipments and track the location of the samples. ColdFusion is used to post the manifests on the study web site for download, enter the manifests into the specimen tracking system and to create the csv file for use in Peernet. Peernet is utilized to create the shipping manifest as a pdf with bar-coded sample IDs.

The T1DGC CoC teams developed a system to support the study DNA Repositories and permit more efficient sample processing with fewer errors. This reduces the repository staff time required to process large sample shipments.

P 105
USABILITY OF COMPUTER-ASSISTED SAQS FOR COLLECTION OF SOCIALLY SENSITIVE DATA
Mona Duggal1,2, Amy C. Justice1, 2, Woody Levin2, and Cynthia Brandt1,2
1Yale University, New Haven, Connecticut, USA
2VA Connecticut Healthcare System, West Haven, Connecticut, USA

Objective We hypothesize that patients in a general outpatient clinic, irrespective of their level of computer proficiency, will give equivalent response to socially sensitive questions, examining alcohol, substance abuse, sexual behavior, and depression, on using computer assisted self administered questionnaires (SAQs) having similar interface as paper based SAQs.

Research Design This is a pilot study using a randomized, crossover design.

Methodology The study is a single center study to be conducted at the general medicine outpatient clinic and women's health clinic in West Haven Veterans Health Administration Hospital. We plan to enroll around 100 patients and require 50 participants to complete the study. Each participant will complete two phases in the study. In the survey phase, participants will complete the computer assisted SAQs and paper based SAQs in randomized order. The SAQs will include questions on alcohol behavior, sexual behavior, substance abuse, depression, technology experience, computer usability and anxiety, health literacy. After completing the questionnaires a member of the research team will debrief the participants and ask for the participant feedback to determine the acceptability and perceived risk of filling computer assisted SAQs as compared to paper based SAQs. Time to complete each questionnaire will be recorded. The primary study outcomes are speed, accuracy, consistency of response, and correlating them with technology experience, computer usability, anxiety, health literacy perception of ease of use, and risk assessment of computer assisted SAQs.

Clinical Findings This is a new study and there are no findings till date. Potential Impact: This study is expected to provide new information regarding barriers and facilitators in utilizing information technology among veterans especially with limited computer proficiency to collect more accurate data on socially sensitive risk behavior thus facilitating better and informed policy decisions on health care.

P 106
USING BASELINE CHARACTERISTICS TO PREDICT RELIABLE PARTICIPANT FOLLOW-UP
Elizabeth Avery, Imke Janssen and Glenda Kravitz
Rush University Medical Center, Chicago, Illinois, USA

Participant follow-up is crucial in longitudinal studies. Using easily collected demographic and medical information at baseline to predict reliable participant follow-up could help studies target their resources more efficiently. The Heart Failure Adherence and Retention Trial (HART) was a randomized trial of 902 heart failure adults in the Chicago metropolitan area. Participants were followed for three years with a telephone contact every 3 months to assess hospitalizations and to update contact information. The percentage of expected contacts completed ranged from 0% to 100%, with a mean of 74.4% and a standard deviation of 22.6%. A participant's death or the study ending before their three years of follow-up was completed reduced the expected contacts. Sixteen participants
died before their first contact was due. Four participants with missing data were excluded. To investigate which baseline characteristics where associated with the percentage of follow-up contacts completed, the remaining 882 participants were divided into 3 completion sub-groups: 0–50%, 50–85%, and 85–100%. We ran an ordinal logistic regression model using SAS 8.2. All demographic information as well as baseline measures of co-morbidities, self-reported physical activity, six minute walk distance, and NYHA class were considered for this model. The following participant characteristics predicted a higher percentage of contacts: older age (p = .0002), being female (p = .0004), or having some education beyond high school (p = .053). Older participants with three or more co-morbidities were more likely to complete a lower percentage of contacts than someone of similar age (p = .026).

In planning studies of chronic disease, more time and resources are important for older participants with multiple co-morbidities, and that these patients may not be able to complete a longitudinal study lasting several years.

P 107
AN APPROACH TO DEVELOPMENT AND DISSEMINATION OF PATIENT RECRUITMENT MATERIALS FOR A LARGE MULTICENTER CLINICAL TRIAL
Wendy L. McBee1, Judith Stein1, Emily Y. Chew2 and Traci E. Clemons2
1The EMMES Corporation, Rockville, Maryland, USA
2National Eye Institute, Bethesda, Maryland, USA

Development of materials to assist clinical centers with patient recruitment for the Age-Related Eye Disease Study 2 (AREDS2) was collaboration between the Division of Epidemiology and Clinical Research and the Office of Communication at the National Eye Institute (NEI) of the National Institutes of Health and the AREDS2 Coordinating Center (The EMMES Corporation).

AREDS2 recruitment materials included: (1) a news release available in English and Spanish - this was distributed via an extensive media list developed at the NEI; (2) a “swiss cheese” news release containing scripts that could be easily customized for local news outlets; (3) answers for likely questions from patients, researchers, and the media; (4) a video containing “sound bites and b-roll” – this was distributed to sites and via satellite to television stations nationwide - the video included (a) interviews with the NEI Director, the AREDS2 Study Chair and two AREDS participants and (b) an animation of AMD pathogenesis for the public; (5) a “message box” containing salient points - this was developed for investigators at AREDS2 clinical sites in preparation for communication with the media; (6) a media “tip sheet” – this resource provided guidance on generating local publicity; and (7) recruitment posters along with “take-one” participant inserts – these were displayed at AREDS2 clinical sites.

The AREDS2 news release was distributed to general and Hispanic media outlets. Within one month seven print articles, 59 television stories, and 26 online media hits were generated. TV coverage reached about 2.3 million viewers, monthly online hits exceeded 14 million, and print circulation was over 840,000.

P 108
THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS) CLINICAL RESEARCH COLLABORATION (CRC): A PROGRESS REPORT
Anne Lindblad1, Traci Clemons1 and Joanne Odenkirchen2
1The EMMES Corporation, Rockville, Maryland, USA
2The National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland, USA

NINDS-sponsored research funds over 1000 grants involving human subjects research. Approximately 200 are Phase I (20%), II (65%) or III (15%) intervention trials involving 40,000 research subjects. An evaluation of a sample of grants estimates 40% can be conducted in office-based practices without referral. NINDS, an institute of the National Institutes of Health, launched the CRC to speed completion of studies and implementation of results by bringing research to physicians who practice in communities and to their patients. The CRC has developed a website allowing individuals interested in neurological research to register and provide contact information for notification of future studies. The CRC website (www.nindscrc.com) facilitates physician training while providing free CME. Anyone (patients, family members, physicians, others) can use the website to search for clinical research studies, interactively screen for eligibility and locate research sites by distance. Patients can refer their physicians for participation and physicians are compensated for their involvement in training and study execution. Special emphasis is placed on including underserved communities by engaging community leaders and physicians who serve these communities and providing alternatives to the website.

Free CME is provided to physicians for basic levels of research training including good clinical practices and human research protection and for participation in monthly one-hour lunch and learn programs. In the first six months of website activation, 488 people representing 40 states have registered, 92 are physicians and 396 include patients, family members, and other interested individuals. The first NINDS-sponsored clinical research study is open for CRC physician participation. Additional existing and newly funded NINDS-sponsored studies are in the development phase for incorporation into the CRC model.

NINDS Contract HHSN265200523641C
INCREASING THE TREATMENT: PLACEBO ALLOCATION RATIO TO INCREASE ENROLLMENT RATES: A COST-BENEFIT ANALYSIS

Ralitza Vozdolska1, Jeremy Pizzola1, Lisa Simon1, Barbara Bartocci1, Joseph Quinn2, Rema Raman1, Mary Sano3, Leon Tha1 and Steven D. Edland1

1University of California, San Diego, LaJolla, California, USA
2Oregon Health & Science University, Portland, Oregon, USA
3Mount Sinai School of Medicine, New York, New York, USA

**Background**  A higher likelihood of randomization to active treatment may be perceived as an added benefit to participation and may result in more rapid recruitment. Changing the allocation has a cost in terms of sample size, for example a 60:40 allocation requires a 4% larger sample to achieve the same power as a 50:50 allocation, but may reduce trial time and cost if recruitment rates are substantially improved.

**Purpose**  To determine when increasing the allocation ratio has a cost benefit to Alzheimer treatment trials.

**Methods**  Costs to perform trials with 50:50 allocation were compared to costs to perform trials with 60:40 allocation under various assumptions about per subject costs, per day costs, and potential increases in enrollment rate due to the higher allocation ratio.

**Results**  Cost-benefit analysis favored increasing the treatment arm allocation ratio if the resulting increase in recruitment rate was 15% or more. Assuming a 15% increase, a trial with 416 subjects under the 60:40 allocation ratio (0.45 subjects/site/month, 30 sites and costs of $10,000/subject and $2,000/day) would take about 80 days less to recruit and would have the same cost as an equally powered trial with 400 subjects and a 50:50 allocation ratio.

**Conclusions**  The dollar cost of increasing the allocation ratio is potentially modest or even neutral if recruitment rates are improved. We caution however that the effect of allocation ratio on recruitment has not been investigated in the context of Alzheimer treatment trials and may not approach the 15% cost neutral threshold. Cost benefit analysis allows a more informed consideration of the study design effects on total trial costs.

RECRUITMENT LESSONS LEARNED FROM A RANDOMISED TRIAL OF TREATMENTS FOR OVERACTIVE BLADDER (OAB) IN WOMEN AGED 65 AND OLDER

Sue Ross, Vatche Minassian, Olivia Sumabat, Danny Lovatsis, Dante Pascali, Ahmed Al-Badr, May Alarab and Harold Drutz

University of Calgary, Calgary, Alberta, Canada

We carried out a randomised trial to investigate the effectiveness of three times daily immediate release oxybutynin versus once daily extended release oxybutin in community-dwelling women with OAB aged ≥65. Our trial stopped after recruiting 72 women because of recruitment difficulties (sample size estimate: 132). The study found no statistically significant differences in voids per 24 hours (11 vs 11), treatment discontinuation (39% vs 30%), or side-effects (57% vs 51%).

Lessons from the trial

- Barriers to recruitment of older community-dwelling women
  1. Many subjects were screened to each eligible patient. Co-morbidities were a major reason for exclusion.
  2. Clinicians were unwilling to make additional demands on older patients.
  3. Our study made heavy demands: 4 study visits over 12-weeks; patient parking was not available; public transport was fairly inaccessible. OAB patients find travelling difficult, because of urgency to void.

Suggestions for overcoming these barriers

1. Target seniors’ groups or residents of senior housing - they have relevant health problems, but remain reasonably active. Referrals from current participants may provide credibility.
2. Provide incentives: transport and escorts for attending appointments; modest financial payments (older patients may have limited resources).
3. Reduce the demands of the study to a minimum consistent with the needs of the research. We were unable to try such strategies because the resources for the study were limited. Recruitment of older women into trials is important for conditions where this is the target population for the treatment under consideration. However recruitment to such trials is costly and labour-intensive, and adequate budget should be included.

FACTORS ASSOCIATED WITH DROPOUT FROM CLINICAL TRIALS: EXPERIENCE OF THE ALZHEIMER’S DISEASE COOPERATIVE STUDY

Barbara J. Bartocci, Jennifer Emond, Ronald G. Thomas, Leon Thal and Steven D. Edland

University of California, San Diego, La Jolla, California, USA

A better understanding of which factors influence retention rates in clinical trials may enhance recruitment and retention strategies of future trials. Studies with a low dropout rate have increased statistical power, and a reduced likelihood of informative censoring. Hence, focused retention efforts can improve a trial’s power and validity.
Data from a recently completed secondary prevention trial of treatments designed to delay the progression of mild cognitive impaired (MCI) to Alzheimer’s disease (AD) were used to examine predictors of study drop-out. This three-year trial recruited 769 participants from 69 AD Cooperative Study sites in the United States and Canada. By year three, 230 (30%) subjects had dropped out of the study.

Applying the Cox Proportional Hazards model and controlling for treatment, age, gender, and marital status and informant relationship, study investigators found that the risk of drop-out was significantly highest among non-white subjects and lowest among subjects with a college education. Checks of each measure for an interaction with the treatment arms yielded no significant effects. In sum, dropout rates from this AD clinical trial were higher among minorities and those with less education, independently of treatment arms.

These findings suggest that recruitment and retention efforts should give special attention to both minority as well as less-educated subjects who otherwise meet study eligibility criteria. This selective targeting holds promise of improving the power and validity of clinical findings.

P 112

LOGISTICAL CHALLENGES OF INCLUDING A BRAZILIAN SITE IN AN CLINICAL TRIAL BASED IN THE UNITED STATES
Lisa Reeves, Lisa Gravens-Mueller, Myra Carpenter, Joyce McKenny and Iria Okano
University of North Carolina, Chapel Hill, North Carolina, USA

FAVORIT is a multicenter randomized controlled clinical trial designed to evaluate whether treatment with folic acid, vitamins B6 and B12 reduces cardiovascular disease in clinically stable renal transplant recipients with elevated total homocysteine levels. Thirty clinical sites (twenty-seven in the U.S., two in Canada, and one in Brazil) have randomized approximately 4000 participants into the study. The challenges of having an international site such as Brazil include:

1) Language: Communication barriers in telephone and email have been challenging. In addition to translating the protocol, consent materials, and medication labels into Portuguese, communications for training and support must be considered.

2) Costs: Inclusion of an international site incurs higher costs for travel for monitoring visits and training, transporting the study medication to Brazil and biospecimens to the U.S.

3) Logistics: Getting approval from Brazilian governmental agencies for importing study medication and shipment of biospecimens to the U.S. needs to be considered. In the case of NIH-funded trials, inclusion of international sites requires U.S. State Department approval for payment to the site. Lastly, different holidays and cultures may complicate communication and shipments.

4) Analysis: Consideration must be given on whether it is appropriate to pool data for analysis from all countries as there may be differences in the populations. Keys to success include having bilingual collaborators who work diligently through the local regulatory requirements, allocating sufficient resources at both the Coordinating and Operations Centers, and having the enthusiastic personnel of the Brazilian site. The challenges of including a Brazilian site have been worth the effort as this site has randomized 14% of the participants in the study.

P 113

DESIGN AND IMPLEMENTATION OF THE LABS PARTICIPANT WEB SITE
Laurie Koozer1, Stephen Barton1, Steven Belle1, Jo Ann Broeckel Elrod2, Amna Daud3, Faith Ebel4, Bill Gourash5, Joelle Kidder6 and Walter Pories7 for the LABS Consortium
1Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
2University of Washington, Seattle, Washington, USA
3Columbia University, New York, New York, USA
4Cornell University Medical Center, New York, New York, USA
5University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
6University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
7East Carolina University, Greenville, North Carolina, USA

The Longitudinal Assessment of Bariatric Surgery (LABS) study is a multi-center two-phase project initiated in 2004. LABS-1 follows bariatric surgical patients for 30 days after surgery to assess short-term safety; LABS-2 follows a subset of LABS-1 participants for 2 years to determine longer term safety and efficacy. While retaining participants for LABS-2 is essential, an observational study with only annual visits creates a retention challenge. Since previous research (Maldan 2005) indicates that the bariatric surgical population relies on internet for information and to provide a virtual community for study participants, the LABS participant web site was created. After participants are consented into LABS-2, they are given a site-specific username and password. On the main page of the LABS web site, users may click on the “participant” button for access to news items about bariatric surgery, study visit expectations, health/wellness tips, recipes, and links to relevant sites. A United States map lists the locations and descriptions of all participating clinical centers. The web site, designed to be easily modified, will vary in content each month. Specifically, the study coordinators will alternately submit new information to
ensure current content. The design allows for additional features and information as the study proceeds. This may include current data on the LABS study and descriptions of the substudies and 7 funded ancillary studies in which LABS-2 participants may also be asked to participate. The website will track hits to the site by unique IP address to track site-utilization and enable assessment of its impact on retention.

P 114
VALUE OF RECRUITING AT INTERNATIONAL SITES: THE BARI 2D EXPERIENCE
Scott M. O’Neal, Joan MacGregor and Mary Tranchine
University of Pittsburgh, Pittsburgh, Pennsylvania, USA

When faced with difficulties in recruiting patients for clinical trials, going abroad is an appealing option. The experiences of The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study provides a glimpse into the costs and benefits of including international sites.

The benefit to recruitment is clear, with varied reasons why international recruitment is often easier than in the U.S. Nine non-U.S. sites randomized 869 participants while 40 U.S. sites randomized 1499, and the international sites recruited three times as many patients per month, on average, as did the U.S. sites (see table).

<table>
<thead>
<tr>
<th>Country</th>
<th>Sites</th>
<th>Participants</th>
<th>Participants per month</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>40</td>
<td>1499</td>
<td>1.0</td>
</tr>
<tr>
<td>Canada</td>
<td>5</td>
<td>353</td>
<td>1.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>1</td>
<td>356</td>
<td>16.2</td>
</tr>
<tr>
<td>Mexico</td>
<td>1</td>
<td>85</td>
<td>5.0</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>1</td>
<td>65</td>
<td>4.0</td>
</tr>
<tr>
<td>Austria</td>
<td>1</td>
<td>10</td>
<td>0.9</td>
</tr>
<tr>
<td>International Totals</td>
<td>9</td>
<td>869</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Costs in both money and coordinating center staff time are greater. Not only must additional factors and expenses be considered, but also those factors vary among countries and even at different sites within the same country. Each stage in the process has brought its own challenges, from known expenses (e.g. the high cost of shipping study medications) to logistical obstacles (e.g. performing data audits where source documents are in another language) to questions about the generalizability of results. In some cases, these additional costs were too high, and sites could not participate.

In the end, the criteria for success are complex enough that there is no simple formula for deciding if the benefits of including a particular site outweigh the costs. However, the experience of BARI 2D suggests that careful planning and consideration of each factor prior to accepting a site will increase the chances for success.

P 115
TO UPGRADE OR NOT TO UPGRADE: NEEDS ASSESSMENT FOR THE SELECT WEBSITE
Rose Thelus and Elise Cook
UT M. D. Anderson Cancer Center, Houston, Texas

**Background/Aims** Large-scale cancer prevention trials are very expensive to conduct due to the often-required large numbers of participants and lengthy follow-up periods. The Internet has provided novel ways for researchers as well as individuals from various backgrounds to obtain medical information. Existing websites that provide health care information are usually difficult to navigate for individuals with a specific need. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) has over thirty-five thousand men enrolled and a follow-up period expected to last up to 12 years. The SELECT Public Website could be a source of health and study information for SELECT participants with the possible additional benefit of enhancing adherence and retention to the trial. This pilot study was conducted as a needs assessment for enhancements to the SELECT Public Website.

**Methods** A survey instrument was administered to SELECT participants to evaluate Internet usage patterns and content preferences among five varied SELECT study sites: Canadian, Department of Veterans Affairs, two academic centers (Chicago and Houston), Community Clinical Oncology Program. From October 2005 to December 2005, surveys were administered to participants during their follow-up study visits. The survey consisted of eight multiple-choice questions to determine access to and use of the Internet. All surveys were self-administered.

**Results** A total 861 participants were asked to complete the survey. The response rate was 97%. Of the participants who had access to a computer (N = 615), 587 (95%) had access to the Internet and 360 (59%) had access to high speed Internet service. Of those who had Internet access, more than 80% would access the SELECT website monthly or more often if desirable information was available. Those who had Internet access would like to see the following information on the SELECT Website: SELECT updates (57%), men’s health (58%) and prostate cancer information (62%).

**Conclusion** This survey illustrates that most of the SELECT study participants completing this Website Survey instrument had Internet access and were interested in men’s health, prostate cancer and SELECT study information. Also, most of these men would access this Website at least monthly if desirable information was included.
This study's main limitation is the lack of identifying information on the individual survey responses. Further study is needed to determine if enhancing the current SELECT Website with the desired information will improve adherence or retention to SELECT.

P 116
DESIGN AND ANALYSIS OF A COST-EFFECTIVENESS STUDY WITHIN A LARGE, SIMPLE TRIAL: THE ALLHAT TRIAL
Barry R. Davis, Paul A. Heidenreich, Jeffrey A. Cutler, Curt D. Furberg, David R. Lairson, Sara Pressel, Chuke Nwachuku and Lee Goldman
University of Texas School of Public Health, Houston, Texas, USA

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a large, simple, double-blind, randomized, active-controlled trial evaluating the effects of amlodipine, lisinopril, and doxazosin compared with chlorthalidone on coronary heart disease in patients with hypertension and an additional risk factor for cardiovascular disease. ALLHAT was conducted from 1994–2002 and included 42,418 patients from 623 centers in the United States and Canada. Data on mortality, (including cause-specific), major clinical events, quality of life, hospitalizations, office visits, and drug costs were collected within the trial and through national databases and source references. Economic analysis objectives were (1) to estimate the relative effectiveness of the antihypertensive agents on survival, quality of life (QOL), and quality-adjusted life-years (QALY); (2) to estimate the resource usage associated with these agents; and (3) to use this information for a cost-effectiveness analysis with cost per quality-adjusted life-year as the unit of analysis. The doxazosin arm ended early and was not included in this analysis. Initial treatment with chlorthalidone is less expensive than lisinopril or amlodipine, but amlodipine provided a non-significant survival benefit and may be a cost-effective alternative. However, a randomized trial with power to exclude “clinically important” differences in survival will often have inadequate power to determine the most cost-effective treatment. This issue and others arose in developing the base-case, range of values for various costs, sensitivity analyses, and projections of costs and effects beyond the data collection period. Details on lessons learned conducting this economic evaluation within the context of a large, simple trial will be presented.

P 117
A MODULE FOR FAMILIARIZING FUTURE DATA SAFETY AND MONITORING BOARD (DSMB) MEMBERS ON ROLES AND RESPONSIBILITIES: TOWARD PROTECTING CLINICAL TRIAL PARTICIPANTS' SAFETY
Jay Johnson and Dianna M. Milewicz
University of Texas, Houston, Texas, USA

Recent expansion in drug development and the demand for evidence-based health practice has resulted in proliferation of Clinical Controlled Trials (CCTs). Clinical Controlled Trials (CCTs) are widely applied as the assessment standard for effectiveness of health care interventions. Data Safety Monitoring Boards (DSMBs), boards specifically appointed to review and monitor research study participant safety, are becoming a relatively conventional and necessary feature of CCTs. DSMB member appointments usually consist of clinicians and statisticians with expertise in areas related to the one monitored. However, many members appointed to such boards do not have prior DSMB experience and are ill-equipped to serve effectively. Although research on DSMBs suggests formal training is unnecessary, it also suggests DSMBs would be better equipped to function effectively when their members are aware of their roles and responsibilities, as DSMB members. Although currently DSMB members do not need formal training or certification to serve, information modules and programs focused on presenting the responsibilities of DSMB members may ultimately improve the safety, ethical integrity, and uniformity of monitoring of CCTs. In addition, such modules may potentially increase the pool of individuals willing to serve on DSMBs. The purpose of this presentation is to report a brief instructional module specifically developed to inform and familiarize future DSMB members about fundamentals, including the following: DSMB Background and Purpose, Charter, Functions, Membership Principles, Roles, Reporting and Record Keeping and Remuneration, Adverse Events, Empirical Evidence about DSMBs, and Future Challenges for DSMBs. This presentation also reports anonymous reviews from DSMB members about the quality of the informational module. The aim of this work is to develop a module that could provide a future on-line training and certification for proposed DSMB members, much like that which could provide an on-line training and certification for proposed DSMB members, much like that which
Abstracts

440 funders and public health experts as to the incidence, prevalence and outcomes of specific conditions in population subgroups. There is overwhelming evidence that some ethnic groups are associated with increased incidence of diabetes, hypertension, stroke and certain cancers, and that there may be disparities in access to services. Government initiatives are in place to collect ethnicity in the healthcare setting but the accuracy of data has yet to be validated.

CanEth is a feasibility project aiming to identify and evaluate current practice in ethnicity data collection. Ethnicity codes need to be reviewed as well as the methods of collection. Results from the UK 2001 census identified that, of those reporting mixed race, 50% were under 16 years. It is not clear whether this reflects true population changes, i.e. ‘ethnic-mixing’, or inability to distinguish within mixed ethnic sub-groups. Traditionally ethnic data was collected by an observer but there is evidence to show that self-reporting is more accurate. Results from a literature review of ethnicity data collection, alongside an evaluation of cancer patients/professionals’ perceptions and experiences of willingness to provide/collect ethnicity data will be reported. Software is available to identify South Asians, the largest UK ethnic minority group, which we will use to validate existing data. Evidence and recommendations will be used to inform Cancer Research-UK policy makers regarding existing ethnic cancer statistics and to lobby the Government to improve ethnicity collection.

P 119 QUALITY CONTROL TESTING IN CLINICAL TRIALS OF PRECIOUS DRUGS
April L. Kennedy, Dianne Peterson, Gary Eden, Dean Argyres, Carlos Apodaca, Nick Vargo and Jamie Barnhill
VA Cooperative Studies Program, Albuquerque, New Mexico, USA

The Veterans Affairs Cooperative Studies Program CRPCC is responsible for the drug supply needs of clinical trials. The CRPCC is compliant with current Good Manufacturing Practices (cGMP) as outlined in the Code of Federal Regulations. The CRPCC’s quality processes assure the safety of subjects in clinical trials. Quality control testing in clinical trials of precious drugs, either those that are in very short supply or those that are extremely expensive, must be conducted in a manner that utilizes the least amount of product, while still maintaining compliance with cGMP. Quality control tests include drug identification, dosage form potency, content uniformity, dissolution and stability testing. This report outlines and describes, with examples, the many techniques that can be used to minimize drug loss to quality control testing throughout the manufacturing, packaging and distribution chain. These include product sampling techniques, drug sample preparation techniques prior to analysis, analytical methods, trace analysis detection methods and sensitive instrumentation. Methods used in trace analysis include semi-micro high performance liquid chromatography (HPLC), Fourier transformed infrared, near-infrared and Raman spectroscopy, ion-mobilizing spectroscopy, time-of-flight mass selective detection for both HPLC and capillary electrophoresis, and multiple forms of electron microscopy. The goal when working with precious drug product is to reduce waste and loss during required testing. The techniques outlined in this presentation can be used to achieve this goal.

P 120 SUPPORTING CLINICAL RESEARCH THROUGH ORGANIZATIONAL EXCELLENCE
Kathy D. Boardman, Mike R. Sather, Dennis W. Raisch and Grant D. Huang
Department of Veterans Affairs Cooperative Studies Program, Albuquerque, New Mexico, USA

Objective To illustrate how an organizational culture of high performance increases efficiency, effectiveness and quality in the pharmaceutical and regulatory support for national and international multi-center clinical trials. Methods We describe how applying (1) the Malcolm Baldrige National Quality Award Criteria for performance excellence, (2) International Standards Organization (ISO) principles for an effective quality management system, (3) current Good Manufacturing Practice (cGMP) regulations for quality pharmaceutical products and services, and (4) a system of Good Clinical Practice (GCP) guidelines; enhances the assurance and protection of the rights, safety and well-being of patient-volunteers. Results The CGMP and GCP systems provide the foundation for the standardization of processes (regulatory), ISO standards provide documentation of processes (effectiveness), while the Baldrige criteria provide a framework for overall organizational excellence (efficiency) that has helped increase our sustainability, customer satisfaction, efficiency/productivity, employee satisfaction, and regulatory compliance. We support approximately 48 multi-center clinical trials with 1,611 clinical sites, 95,424 patients, and 303 different study drugs and devices. External review and recognition includes nine Baldrige based performance excellence awards and one site visit from the National Baldrige Program. We were certified by ISO in 2003 and subsequently passed three surveillance audits. The CRPCC is registered with the FDA as a cGMP facility and to date has passed every cGMP/GCP audit performed by the FDA and industry.

Conclusions Due to our systems approach of concurrent implementation of GCP, cGMP, ISO, and Baldrige, we have demonstrated high performance and increased capability.
**Objective**  To demonstrate the key pharmaceutical processes to meet and exceed customer requirements in multi-center clinical trials.

**Methods**  Our key processes are driven by customer requirements and deliver increasing value by applying (1) the Malcolm Baldrige National Quality Award Criteria for performance excellence, (2) International Standards Organization (ISO) principles for an effective quality management system, and (3) current Good Manufacturing Practice (cGMP) regulations for quality pharmaceutical products and services.

**Results**  Our key value processes of service, product and business in clinical trials are (1) design and conduct, (2) manufacture, package and label drugs/supplies, (3) conduct trials through project management, respectively. Utilizing Baldrige, ISO, and cGMP we achieve near zero defects while meeting regulatory requirements with an annual 0 to 2.2 parts per million shipping defects over the last 5 years which is well below six sigma standards. Our service and product processes directly contribute to our productivity and sustainable growth. We approach the number one market leader in productivity per employee and exceed companies ranked 2 through 4 in 2004 at $163,206 per employee. We sustain an annual funding growth rate of 10% over the last 5 years. Our business process of project management enables our teams to manage complex clinical trials, multiple deadlines effectively and achieve 100% performance to budget for the past two years.

**Conclusions**  Utilizing Baldrige, ISO, and cGMP, we developed quality systematic processes to achieve high performance and increased capabilities.

---

**P 122**

**ANALYSIS STRATEGIES FOR IMMUNOLOGIC ENDPOINTS IN CANCER IMMUNOTHERAPY TRIALS**

Heidi L. Weiss, Meng-Fen Wu, Doug Myers, Clio Rooney, Malcolm K. Brenner, Helen E. Heslop and Catherine M. Bollard

Baylor College of Medicine Houston, Texas, USA

**Introduction**  Cancer immunotherapy trials using adoptively-transferred antigen specific T-cells have low toxicity profiles. As such, a major objective of early phase trials is evaluation of T-cell expansion, persistence, and immune reconstitution. We present analysis strategies to model and estimate these immunologic endpoints.

**Methods**  Phase I immunotherapy trials in patients with Hodgkin’s Disease and neuroblastoma were utilized. EBV and LMP2-specific T-cell levels were measured over time and plotted to graphically illustrate kinetics of immunologic responses. We modeled longitudinal measurements using piecewise random coefficient mixed models, bivariate mixed models, and nonlinear mixed models. Treatment effects were estimated and comparison of models was performed using goodness-of-fit statistics.

**Results**  Plots of T-cell levels had a general pattern of expansion, decline and stabilization. Estimates from the piecewise linear mixed model showed a positive slope representing the expansion of T-cells during the initial phase and a negative slope during the second phase of decline and stabilization. This was extended into bivariate mixed models to simultaneously model different T-cell populations. Larger slopes indicating better expansion were observed in the T-cell population specific to the target tumor antigens. Nonlinear mixed models using exponential decay function provided parameter estimates of maximum, minimum, and decay rate of T-cell levels. AIC statistics indicated slightly better fit for the piecewise linear mixed compared to nonlinear mixed models.

**Conclusion**  The kinetics and magnitude of T-cell expansion and decline varied by patient population, treatment regimen, and specificity of T-cells. The linear models provided slightly better fit while use of nonlinear functions gave additional information concerning patterns of immune reconstitution. Analysis strategies should be explored to accurately estimate biologic endpoints to better design immunotherapy trials.

---

**P 123**

**BEFORE AND AFTER: ‘CRITICAL EVENT’ ANALYSIS WITH LONGITUDINAL DATA USING SAS**

Robert L. Bauserman and Douglas Thompson

Maryland Medical Research Institute, Inc., Baltimore, Maryland, USA

In large samples followed over time, a ‘critical event’ of interest may occur (such as pregnancy or disease diagnosis or movement of a measurement value past a threshold). This event may be present for some subjects, but not others, and may take place at different points in time for different subjects. Analyses of critical events, their predictors, and sequelae may require examining specific predictors or outcomes on the basis of when they occur, relative to the critical event. However, the critical event may occur at different timepoints for different study participants. This makes it necessary to correctly identify and mark when observations occur relative to the critical event, so that later modeling or other analyses can make comparisons or predict outcomes at similar intervals before/after the critical event for all subjects.
This presentation includes SAS macros and code that, starting from a multiple-observation-per-subject dataset (one observation per visit), will (a) mark the age/timepoint at which the critical event occurs in those who experience the event (‘onset time’), (b) identify appropriate control subjects and assign them an ‘onset age’ to provide comparison points and (c) order a repeated outcome measures in terms of time/number of measurements before or after the critical event.

The result is a single-observation-per-subject dataset that allows analysis of outcomes at specified intervals before or after the critical event, regardless of the age/timepoint at which the critical event occurred for each subject.

**P 124**

INFLUENCE ON HODGES-LEHMANN ESTIMATION OF IMPUTED VALUES FOR WORST RANK ASSIGNMENT: A CASE STUDY

Matt Downs and Joel Verter
Statistics Collaborative, Inc., Washington, D.C., USA

When comparing group differences for continuous outcomes, the mean is the most frequently used summary statistic, allowing for easy calculation of mean differences and confidence intervals. For some variables, however, the mean may not be the most appropriate summary statistic. In these cases, a non parametric statistic, e.g., the median, may provide a better summary. Use of the median, however, requires a more complex method of estimating the difference between medians and its confidence interval.

The Hodges-Lehmann (HL) estimate for the difference between two groups provides a non parametric measure of group difference. As a non-parametric measure of effect, it often accompanies the results of non-parametric statistical tests, such as the Wilcoxon rank-sum test. The HL estimate can be viewed as a measure of the degree to which one distribution is shifted relative to another. Although based on ranks, the HL estimate and its confidence interval are affected by the actual values within the distributions of the two groups.

This presentation provides a case study of the use of the HL estimator to provide a measure of association for group differences in six-minute walk distance, a measure of cardiovascular health. To account for missing data, the analysis assigned the worst rank (WR) to subjects who lacked a measurement because of death and assigned the second worst rank (SWR) to subjects lacking a measurement for other reasons. The presentation will summarize the potential effect on the HL estimator of varying the actual numeric value assigned as the WR and SWR.

Conclusion: When using the HL estimator in an analysis requiring imputation of missing values, evaluate the impact of the values used for imputation.

**P 125**

A WEB-BASED APPROACH TO ADJUDICATION MANAGEMENT IN A CLINICAL TRIAL

Carrie C. Williams, Patricia Hogan, Jerry Barnes, Patricia Feeney, Cora Lewis, Karen Johnson and the Look AHEAD Research Group
Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA

Adjudication of disease-specific study outcomes is a critical component in the conduct of clinical trials. Management of this process includes monitoring medical records submissions from clinical sites, distribution of cases among numerous physician adjudicators, coordination of multiple levels of disagreement resolution, and handling requests for additional medical records while meeting goals for timely completion. We report on the design and success of an automated adjudication management and batching system that was developed for Look AHEAD (Action for Health in Diabetes). Look AHEAD is a 16 center clinical trial with 5145 overweight or obese participants who have Type 2 diabetes. The primary objective of the study is to assess the long-term effects of weight loss on serious cardiovascular events.

We utilize a web-based batching system to manage the adjudication process (currently about 800 cases per year). Case specifics are logged and displayed on a registry which promotes tracking of all cases in a batch at a glance. A status report provides adjudicators with information regarding pending and adjudicated cases for participants whose cases are included in the batch. Adjudication forms are compared electronically based on rules set by the Adjudication Committee and a report is generated indicating the next step in the complex process of disagreement resolution. The system captures the adjudication history for cases requiring multiple resolution levels. Reports track the length of time from receipt of cases at the Coordinating Center until completion and agreement rates for adjudicators.

The Look AHEAD web-based adjudication management system is a useful tool for supporting, monitoring, and documenting the adjudication process while providing pivotal information for adjudicators.
P 126
EMPLOYING GEOGRAPHIC INFORMATION SYSTEMS TO ASSESS THE EFFECTS OF TRAFFIC EXPOSURE ON RESPIRATORY FUNCTION OF CHILDREN WITH ASTHMA
John C. Schwarz and Herman Mitchell
Rho Inc., Chapel Hill, North Carolina, USA

Recently, researchers have shown that outdoor pollution can reduce pulmonary function, especially among children with asthma. One of the primary sources of pollution in inner-city urban areas, where asthma rates are unusually high, is automobile and truck traffic. In seven major urban areas, the NIH/NIAID Inner-City Asthma Study (ICAS) examined a population of 937 inner city children with asthma to assess the impact of pollution on respiratory function. Pulmonary function measurements were collected over two week periods at six month intervals for the duration of the two year study. These measures included Forced Expiratory Volume in 1 second (FEV1) and Peak Expiratory Flow (PEF).

We explored the utility of geographical information system (GIS) software, to determine the distance of children’s homes to roadways in order to establish traffic exhaust levels and their impact on pulmonary function. A measure of road density by zip code and the number nearby EPA-listed stationary pollution sources were also examined for their usefulness as predictors of pollution related to respiratory function. Indoor measures of NO2, a marker of traffic pollution, were taken in a subset of 341 homes to validate the accuracy of the more general GIS approach to measuring traffic pollution exposures.

The analysis revealed significant associations between pulmonary function in relation to distance from major roads. The GIS approach accurately predicted indoor direct measures of NO2. Differences across urban areas with regard to stationary pollution sources suggest the importance of this additional source of urban pollution exposure.

P 127
PREDICTING INDOOR PARTICULATE MATTER FROM OUTDOOR PARTICULATE MATTER AND OTHER MEASUREMENTS IN THE INNER-CITY AIR POLLUTION STUDY
Miguel Villarreal, Agustin Calatroni and Herman Mitchell
Rho, Inc., Chapel Hill, North Carolina, USA

Exposure to particles may cause or exacerbate asthma morbidity in inner-city youth. Children spend a majority of time indoors where exposure to harmful particles occurs. Direct measurement of indoor exposure is costly and difficult to obtain. However, outdoor particulate matter exposure data is readily available for most U.S. cities. A model that predicts indoor particulate matter concentration from outdoor levels and other accessible data would enable investigators to examine the effects of indoor particulate exposure on asthma morbidity when indoor measurements are unavailable.

The NIAID/NIEHS Inner-City Air Pollution Study characterizes exposure levels and sources of fine particulate matter (particulate matter less than 2.5 microns—PM2.5) in the homes of 302 inner-city children with asthma. Continuous measurements of indoor PM2.5 were collected for each child for two weeks, at three visits, at six month intervals. Information detailing possible sources of PM2.5 such as smoking, cooking, and cleaning activities was also collected. These data, along with daily outdoor PM2.5 measurements gathered from the EPA’s Aerometric Information Retrieval System (AIRS), are used to develop a predictive model of indoor PM2.5.

This analysis is twofold. Firstly, a bootstrap technique is used for variable selection. Once variables with prognostic value in predicting indoor PM2.5 are identified, they are incorporated in a final, linear mixed model. The second part of the analysis is to evaluate the predictive qualities of the model by using a stratified, 10-fold cross-validation technique and examining prediction values through statistical and graphical analysis. If it can be established that indoor PM2.5 can be predicted from outdoor PM2.5 accurately, the cost and inconvenience of collecting indoor exposure data can be minimized in future studies.

P 128
A NEW METHOD FOR THE SAMPLE SIZE CALCULATION FOR THE THOROUGH QT/QTC STUDY
Shu Zhang
Sepracor, Inc., Marlborough, Massachusetts, USA

The ICH recently issued a guideline (E14) to the pharmaceutical industry to address QT interval prolongation. The guideline proposed conducting a “Thorough QT/QTC Study (TQS)” and defined criteria for a “negative TQS”. Several methods have been proposed for the sample size calculation for the TQS. However, most methods only considered mean change instead of the maximum change as defined by the guideline. In addition, the impact of the negative TQS criteria on the traditional framework of hypothesis testing was not examined.

In this work, we discuss the ambiguity of the negative TQS criteria, and demonstrate that for the TQS, using hypothesis testing as the framework for sample size calculation is inadequate. Using the distribution function of maximum change derived in this work, we propose a unified approach for the sample size calculation specifically...
designed to address the negative TQS criteria. We then calculate the sample size based on different assumptions, compare our results with those obtained through hypothesis testing, and show that the hypothesis testing method always underestimates the required sample size.

P 129

GRAPHICAL DISPLAYS OF TARGETED ADVERSE EVENTS
Robert B. Fowler and Neil Wohlford
Statistics Collaborative Washington, DC., USA

Often in safety reporting and monitoring in Phase III clinical trials, certain events of special interest are identified in advance based on earlier studies or concerns regarding a therapy’s mechanism of action. These targeted events may be part of the formalized interim stopping guidance. Common presentations include tabulations by body system and coded term as well as listings that present the event details in chronological order by patient. However, these non-graphical displays are limited. The tabulations cannot easily present how many patients have had multiple events and the duration of events. Incorporating the severity of the events, study therapy exposure, and response to study therapy will overwhelm the presentation. In addition, data listings cannot present as much information at once and thereby limit the ability of the reviewer to summarize across patients.

We have developed graphical displays of targeted events that attempt to incorporate each of the aforementioned aspects. In particular, we feel the benefit to these displays is the ability to weigh the benefits of study therapy against the risk of the side effects to therapy. Such an evaluation is particularly important within the context of oncology or antipsychotic therapy trials. Several mocked examples based on ongoing Phase III studies are presented.

P 130

SAMPLE SIZE CONSIDERATIONS IN DESIGNING A STUDY TO COMPARE THE REPRODUCIBILITY OF 2 END-POINTS IN A CLINICAL TRIAL
Paula L. Friedenberg and John Lachin on behalf of Type 1 Diabetes TrialNet
The George Washington University Rockville, Maryland, USA

It is desirable to determine the reproducibility of a measure used as an outcome in clinical trials. The Type 1 Diabetes TrialNet conducts studies in new-onset Type 1 diabetes mellitus to evaluate efficacy of immunosuppressive or immunomodulatory agents to preserve beta cell function (insulin secretory capacity), measured indirectly using plasma C-peptide concentrations in response to 2 distinct stimuli. TrialNet designed a study to compare the reproducibility of 2 different tests: the mixed meal tolerance test (MMTT) and the glucagon stimulation test (GST). Each subject is randomized to receive 2 different tests, repeated twice, with either of the following order: AABB or BBAA. Not all subjects comply; some only receive 3 tests before termination. A simulation model was utilized to determine the sample size required for 3 scenarios of percentages of subjects estimated to terminate early.

The following sample sizes would be required for different scenarios:

<table>
<thead>
<tr>
<th>ρ(Test 1)</th>
<th>ρ(Test 2)</th>
<th>Corr (Test 1, Test 2)</th>
<th>Power</th>
<th>100% have 4 tests N</th>
<th>80% have 4 tests, 20% 3N</th>
<th>60% have 4 tests, 40% 3N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90</td>
<td>0.785</td>
<td>0.5</td>
<td>90%</td>
<td>108</td>
<td>116</td>
<td>120</td>
</tr>
<tr>
<td>0.80</td>
<td>0.594</td>
<td>0.5</td>
<td>90%</td>
<td>104</td>
<td>114</td>
<td>120</td>
</tr>
<tr>
<td>0.70</td>
<td>0.424</td>
<td>0.5</td>
<td>90%</td>
<td>100</td>
<td>114</td>
<td>116</td>
</tr>
</tbody>
</table>

For N of 108 having all 4 tests, there are a total of 432 tests. With 116 subjects, of whom 80% have 4 tests and 20% have 3, there are a total of 441 tests. For 120 subjects, of whom 60% have 4 tests, 40% have 3, there are a total of 432 tests. Thus, between 432 and 440 total tests are required to provide 90% power.

P 131

TEACHING THE CODE OF FEDERAL REGULATIONS IS NOT A GAME BUT LEARNING THEM CAN BE
Nina M. Trocky
University of Maryland Baltimore, Maryland, USA

Graduate nursing students enrolled in the Clinical Research Management (CRM) specialty program must ultimately command a thorough knowledge of the Code of Federal Regulations (CFRs). Learning the CFRs, however, may not be viewed as an exciting endeavor. We addressed this challenge by incorporating the development of The Code of Federal Regulations Jeopardy Game into the course requirements. Additionally, we blended active learning theory with curriculum development to engage the individual and collective energies of the nursing students through the game development process. In the end, we accomplished two objectives: (1) developed a game called Code of Federal Regulations (CFR) Jeopardy in MS PowerPoint to serve as a training module for nurses engaged in clinical research and (2) increased the knowledge level with respect to the CFRs of the nursing students participating in the game development process.

Clinical Trials 2007; 4: 371–455
http://ctj.sagepub.com
There is no disputing the fact that traditional didactic educational approaches may serve this purpose. Alternately, active learning strategies engage students in participatory learning. Students become active participants rather than passive observers. They must make decisions, solve problems, and react to the results of their decisions. Our approach to education blended the appreciation of the adult learner with course expectations and requirements while establishing a forum for students to direct their learning experience. The CFR Jeopardy Game was developed during a course with this goal in mind.

Student motivation can increase with the use of games as one means to reinforcing skills and key concepts. Adult learning theory integrates new learning with professional experience focusing on practical and relevant information. This poster describes how we accomplished both plus the production of a portable training module that can be utilized in other clinical research oriented courses.

**P 132**

Student Scholarship Honorary Mention

BAYESIAN SCREENING FOR PHARMACOGENETIC EFFECTS IN CLINICAL TRIALS

Nlengey Gus and Daniel F. Heitjan
University of Pennsylvania Philadelphia, Pennsylvania, USA

Pharmacogenetic studies seek to detect genetic markers that modify treatment effects. Thus, statistical methods for pharmacogenetic studies aim to assess the significance of treatment-bymarker interactions. For example, with data from a randomized clinical trial, a potential approach is to build a statistical model to predict outcome from genotype, treatment indicator and their interaction, and to measure evidence by testing the significance of the interaction coefficient. When the number of potential markers is large, however, we encounter the problem of multiplicity of tests. In this article we address the problem of multiplicity by proposing a Bayesian method to screen for significant genetic markers. The method is based on Bayesian hypothesis testing (Berger, 1985) and evaluates evidence using Bayes factors. We show how to carry out the computation using both importance sampling and analytical approximation. An advantage of the Bayesian method is that it explicitly incorporates prior information, which is not possible in conventional frequentist tests. Moreover, the Bayesian criterion (Kris and Raftery, 1995) is more conservative than the uncorrected conventional frequentist test, but less conservative than a conventional frequentist test with a Bonferroni-type correction. We apply our method to a randomised trial of pharmacotherapy for smoking cessation, in which a number of SNPs were evaluated as potential pharmacogenetic markers. We compare our approach with uncorrected and corrected frequentist approaches.

Key words: Bayes factor; Bayesian hypothesis test; bupropion; importance sampling; nicotinereplacement therapy; pharmacogenomics; single-nucleotide polymorphism; Laplace approximation

**P 133**

A (SOMewhat) AUTOMATED APPROACH TO CREATING A DMC REPORT

Deborah N. Wentworth
University of Minnesota Minneapolis, Minnesota, USA

Preparation of a comprehensive DMC (Data Monitoring Committee) report is a time-consuming task. Because of the confidential nature of the material, the statistician creating the report often is also responsible for formatting or assembly tasks that might otherwise be performed by administrative support staff. This presentation describes an approach for automating some of the steps of producing a DMC report. Analyses for the report are written using SAS software which outputs tables and graphs to individual RTF files. A combination of in-house macros and standard SAS procedures using Output Delivery System (ODS) features are used to format tables with shading, bold fonts, and other formatting techniques that improve readability of resulting tables. At the time of report, a shell script runs all the applicable analysis programs. Next, a SAS macro is run that collates the tables and graphs, labels and numbers them, and saves them in one large WORD document. Narrative is added to the document. Finally, a list of tables and figures, with corresponding page numbers, is automatically generated using tools available within WORD.

Adoption of these techniques has proved useful in the production of DMC reports for AIDS trials conducted by the Division of Biostatistics at the University of Minnesota. Compared to previous procedures used within our organization, this process takes less time and results in a more professional-looking, user-friendly document.

**P 134**

A SAS MACRO USED TO SUMMARIZE MEDDRA-CODED ADVERSE EVENTS

Deborah Wentworth, G. Grandits and G. Thompson
University of Minnesota Minneapolis, Minnesota, USA

MedDRA (Medical Dictionary for Regulatory Activities) coding of adverse events (AEs) is becoming a common and sometimes required method of summarizing safety data in clinical trials. In the MedDRA system, AEs are coded using a database of numeric codes that correspond to a hierarchical logical tree structure of Lower-Level Terms,
Preferred Terms, High-Level Terms (HLTs), High-Level Group Terms, and System Organ Class. Several approaches have been adopted to summarize MedDRA-coded AEs for Data Monitoring Committee reports. This paper describes one such approach, where our aim is to compare treatments groups at the HLT level, dynamically analyzing only HLT events which occur a pre-specified number of times.

The incidence of common HLTs is summarized by treatment group using a SAS macro that automates the process. After study data are reshaped in the format needed for analysis, the number of patients who experience events corresponding to each specific HLT is determined. For events which are “common” (occurring in at least 6 patients in either treatment group in this example), event incidence and significance testing is performed. If either treatment group has zero events, Fisher's exact test is used to calculate p-values; otherwise, hazard ratios and p-values are calculated using proportional hazards regression models. Finally, the ODS (Output Delivery System) features of SAS are used to produce formatted tables that are easily imported into WORD documents.

This macro has proved useful for ongoing AIDS trials conducted at the Division of Biostatistics at the University of Minnesota. The macro can be easily changed to summarize events at a different level of the MedDRA tree, or to adjust the threshold used to determine “common” events. A partial table is displayed below:

<table>
<thead>
<tr>
<th>MedDRA HLT</th>
<th>Group A No. Rate</th>
<th>Group B No. Rate</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal and gastrointestinal infections</td>
<td>8</td>
<td>10</td>
<td>0.66 (0.26,1.68)</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3</td>
<td>2.41 (0.65,8.94)</td>
<td>.19</td>
</tr>
<tr>
<td>Acute and chronic pancreatitis</td>
<td>0.08</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.09</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**P 135**

A STRATEGY FOR DATA MONITORING IN A PUBLICLY SPONSORED, LARGE, MULTI-CENTRE, INTERNATIONAL RANDOMISED CONTROLLED TRIAL

Sarah Edwards

University of Toronto, Toronto, Ontario, Canada

According to International Conference on Harmonisation Good Clinical Practice guidelines, there is a need for on-site monitoring throughout a clinical trial. However, with publicly funded, large, multi-centre, international randomized controlled trials there is often not a sufficient budget for such visits.

The Early External Cephalic Version 2 Trial (EECV2), designed to compare whether early ECV (at 340/7–356/7 weeks) versus delayed ECV (not before 370/7 weeks) increases or decreases the likelihood of caesarean section for women with a fetus in breech presentation, is one such large, multi-centre, international RCT that has been funded by the Canadian Institutes of Health Research.

A strategy was developed for EECV2 in which data monitoring is conducted in conjunction with site visits by the Principal Investigator to promote the trial and collaborators' meetings in international locations. Centres not well known to the Steering Committee are prioritized for site/monitoring visits.

A data worksheet specific to non-drug trials was developed which satisfies the purposes of monitoring: to verify that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendments, with GCP, and with the applicable regulatory requirements. This presentation details the initiation of the strategy, the creation of the data worksheet and the evaluation of the process. Five site/monitoring visits have been conducted with positive results.

The data worksheet proved to be useful and several more site/monitoring visits are planned for April 2007.

**P 136**

THE EFFECT OF INCENTIVES AND HIGH PRIORITY MAILING ON POSTAL QUESTIONNAIRE RESPONSE RATES: A MINI-RCT

Laura Kenton1, Cindy-Lee Dennis1, Julie Weston1, and Alex Kiss2

1University of Toronto
2Sunnybrook Health Sciences Centre, Toronto, Canada

**Background** Postal questionnaires are used frequently in research trials. Evidence exists that strategies can be used to increase response rates.

**Objectives**: To assess the impact on questionnaire response rates of 1) a small monetary incentive versus a lottery, and 2) increasing perceived importance by adding a 'high priority' stamp to the mailing envelope, for participants in the Postpartum Depression Peer Support Trial.

**Method** Participants in the peer support group were mailed a questionnaire to evaluate their experience. In our mini-RCT they were randomized to: 1) monetary incentive alone; 2) monetary incentive and 'high priority'
mailing; 3) lottery alone; or, 4) lottery and ‘high priority’ mailing. The monetary incentive ($2 coin) was mailed with the questionnaire. The lottery was a draw for a $50 gift certificate upon questionnaire receipt. All questionnaire packages included: 1) a brightly coloured cover page; 2) a letter signed by the Principal Investigator on University letterhead; 3) a hand written address on envelope; and, 4) stamps rather than franked return envelopes.

**Results** At the time of analysis, 81% of the questionnaires had been mailed. The overall response rate was 75%. A logistic regression was run to determine whether there were differences in the proportion of responders between groups. The analysis indicated no significant differences between groups ($\chi^2 (3) = 3.77, p = 0.29$).

**Discussion** Results suggest that the monetary incentive and lottery yielded the same response rates. The use of a ‘high priority’ stamp did not increase response rates.

<table>
<thead>
<tr>
<th>Response</th>
<th>Group (n)</th>
<th>Yes (n)</th>
<th>No (n)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>53</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>53</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>48</td>
<td>23</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>55</td>
<td>14</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>209</td>
<td>72</td>
<td>281</td>
</tr>
</tbody>
</table>

**P 137**

**THE PROCESS OF OBTAINING CONTRACTUAL AGREEMENTS AND TRANSLATIONS IN A 5 YEAR FOLLOW-UP STUDY**

Edna Kavuma, Laura Tomat, Sheila Hewson, Elizabeth Asztalos and B. Anthony Armson

University of Toronto Toronto, Ontario, Canada

The Multiple courses of Antenatal Corticosteroids for preterm birth study: A 5 year Follow-up (MACS-5), is designed to determine the long term effects of repeat courses of antenatal corticosteroids on children whose mothers were randomized into MACS (Multiple courses of Antenatal Corticosteroids for preterm birth study). When each child is 5 years of age, a parent-administered questionnaire will be used to assess attention, memory and behavioral skills. A physical examination will also determine, from a clinical perspective, the presence of cerebral palsy or other neurosensory deficits.

As MACS-5 is an international, double masked, multicentre trial, it is imperative that the assessment tools being administered meet the language and cultural needs of the families involved. This presentation will further describe the challenges faced in reaching contractual agreements and obtaining translations while establishing the study.

Contractual agreements were needed in order to format each test into one document that would then become the ACS-5 parent-administered questionnaire. Additional agreements were executed with the authors of the psychological tests to allow for translation of the questionnaire into various languages. The questionnaire was then designed in a scannable format to allow for data entry and use of data verification software.

The translations required included: Arabic, Danish, Dutch, French, German, Hebrew, Hungarian, Mandarin, Polish, Portuguese, Russian, and Spanish. Subsequent back-translations were provided by local and international contacts. To further ensure validity of the tests was maintained, back-translations were then submitted to the test authors for approval. Over the past year, 9 of the 12 required translations have been completed and remaining languages are being finalized.

**P 138**

**GETTING THE BALANCE RIGHT WHEN ESTABLISHING A NEW RESEARCH THEME IN A NEW TRIALS UNIT**

Robert Millwood, Janet Dunn, Sarah Duggan and Sallie Lamb

University of Warwick Coventry, UK

Warwick Medical School (WMS) is one of the five new medical schools within the UK, established in 2000, based in one of the UK’s leading research universities rated fifth in the country in the government’s last research assessment exercise. Warwick Clinical Trials Unit is an academic unit undertaking clinical trials addressing real issues of local, national and international importance. The areas of research have been recently expanded to include cancer clinical trials.

Warwick Medical School collaborates closely with the local Arden Cancer Network serving a population of around one million people based within the University Hospital Coventry and Warwickshire (UHWC). Infrastructure support is available through the National Cancer Research Network for screening patients to check eligibility for suitable trials and carrying out informed consent. However support is very limited for developing new trials. Trial development needs to be carried out within the constraints of the academic support within WMS and requires external funding.
Our experience of establishing cancer as a research theme, in particular balancing the real costs of research against the available funds for research will be discussed. Only with the infrastructure support from WMS, has it been possible to establish a statistical centre for five ongoing trials and develop a program for head, neck and breast cancer. The maximisation of the financial and personnel support will be explained. The invaluable use of established networks and integrating with these for the benefit of patients and region trials will also be outlined. Implementation of new technologies to aid the randomisation of patients will also be explained and the cost saving benefit it can provide.

P 139
IMPACT OF HURRICANE KATRINA ON THE SELENIUM AND VITAMIN E CANCER PREVENTION TRIAL (SELECT): PREPARING FOR DISASTERS THAT AFFECT CLINICAL RESEARCH
Elise Cook1, Karen Anderson2, Sandra Hamilton3, Sarah Moody Thomas4 Russell Campbell5 and Katie Arnold5
1UT M. D. Anderson Cancer Center, Houston, Texas, USA
2Seattle, Washington, USA
3Atlanta, Georgia, USA
4New Orleans, Louisiana, USA
5Seattle, Washington5, USA

SELECT is a prostate cancer prevention trial conducted at over 420 sites in the US, Canada and Puerto Rico with 35,534 randomized men. The 2005 hurricane season affected several SELECT sites. The lessons learned from these sites can be a resource for others preparing for future disasters. Although many institutions have disaster plans, research is typically a low priority. A Research Disaster Plan (RDP) is needed to address unique research requirements. During a SELECT training workshop, SELECT staff from two New Orleans sites presented their experiences with hurricane Katrina. Their experiences were intended to motivate SELECT’s other sites to review their disaster plans. Emergency Services and Homeland Security officers were also available for one-on-one consultation. In the months after the training workshop, SELECT sites did make many significant changes to their local RDPs. We will present the various issues faced by the study sites affected by hurricane Katrina, such as personnel issues, communication difficulties, access to the study sites and study resources, and the inadequacy of the existing RDPs for the 2005 hurricane season disasters. The resulting changes made by the SELECT sites and Statistical Center will be discussed, such as adding out of town family and friends contact information for study participants as well as future evacuation plans for research staff.

P 140
THE ROLE OF PRACTICE BASED RESEARCH NETWORKS (PBRN) IN THE SPECTRUM OF CLINICAL TRIALS
Frederick A. Curro
The PEARL Network New York, New York, USA

Practice Based Research Networks (PBRNs) emerged in the late 1970s to address medical practitioners’ concerns about healthcare delivery. Recently the National Institute of Dental and Craniofacial Research (NIDCR) has committed seven years of funding to extend that model to dentistry by supporting PBRNs comprised of private practitioners. Clinical studies appropriate to the PBRN model range between surveys, chart reviews, and to a limited extent, Randomized Control Trials. These protocols are primarily standard-of-care studies designed to gather data on the prevalence of disease states and/or to optimize patient care delivery. PBRNs can also be used for drug safety and pharmacovigilance studies as these data are captured as part of the routine dental patient history. PBRN studies may be limited in scope by what is actually feasible operationally in the private dental office. The primary goal of PBRN studies is to have immediate relevance to the care of dental patients. The data collected by practitioners is designed to fit the office protocol and dynamics and to stimulate additional questions for further study. The power of the PBRN model lies in the cumulative effect of aggregate data derived from the merged experiences and contributions of individual dentists. The translational time to incorporate the clinical findings within a PBRN should be reduced since the data generated and analyzed are directly related to the dental practices. The research questions are germane to the daily practice of the general dentist practitioner and maintain patient identification as opposed to categorizing them as research subjects. The challenge of the PBRN is in balancing good science with practical operational protocols tailored to the private office environment.

P 141
BARRIERS TO AND FACILITATORS OF EFFECTIVE NETWORK FUNCTIONING: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT
Steve Durako, Paula Darby Lipman and Nancy Dianis
Westat Rockville, Maryland, USA

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with
members of a sub sample of CRNs to gather detailed information about network practices. Interviews were conducted with respondents to identify and explore the barriers and facilitators associated with these practices. A National Leadership Forum was held to bring together the clinical research community to discuss project findings and the feasibility of adapting practices identified as most effective into their own research environments. Valuable insights on barriers, facilitators, and “lessons learned” associated with adoption and implementation of network practices were gained through both the survey data collection and the input from Forum participants. Qualitative findings will be presented regarding how to overcome barriers associated with management, governance, and regulatory issues; data management and information technology, staff training and professional development, and recruitment and retention.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and to stimulate the discussion of possible best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources (NCRR), a component of NIH. It stems from the NIH’s commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.

P 142
BIAS IN WEIBULL REGRESSION WITH SMALL SAMPLE SIZE AND INTERVAL CENSORED TIME-TO-EVENT DATA
Barry S. Eggleston
Rho, Inc., Chapel Hill, North Carolina, USA

A clinical trial designed to study the relationship between a set of proposed therapies and the time until a biomarker event such as seroconversion will produce interval censored time-to-event data. When the outcome is interval-censored, one possibility is to estimate the time-to-event distributions for each therapy and compare the therapies using a parametric survival model such as Weibull regression. Two data analysis issues arise with parametric survival modeling of clinical trial data when the outcome is an interval censored time-to-event measure. The first issue concerns sample size. Parametric survival models use maximum likelihood estimation to estimate model parameters, so the estimators have good statistical properties with large sample sizes. With small sample sizes, however, the estimators are biased, and the bias is propagated to statistics derived from these biased estimators. Also, the effect of sample size on bias is not the same for all estimators and statistics. Using Weibull regression to estimate and compare the time-to-event distributions of two treatment groups, this presentation reports simulation results that illustrate how much bias occurs in the model parameters and the hazard ratio when no censoring occurs. The second issue concerns the possible effect of interval censoring on study results. Does interval-censoring cause any additional bias in the study results? If so, what are some interval-censoring characteristics that affect bias? By reporting simulation results based on Weibull regression to estimate and compare the time-to-event distributions of two treatment groups, this presentation will demonstrate that interval censoring can affect parameter bias beyond the amount attributable to sample size. Also, this presentation will propose a guideline for selecting interval endpoints to minimize the amount of bias imposed by the interval censoring.

P 143
A NEW APPROACH TO CATEGORIZATION AND GRADING ADVERSE EVENTS IN AUTOIMMUNE TRIALS
Lynette L. Keyes-Elstein, Rachel Berry and the ACE Clinical Trials Development Team
Rho, Inc., Chapel Hill, North Carolina, USA

Categorization of adverse events (AEs) using coding ontologies (e.g. MEDRA) generally occurs during the production of the clinical database. Because of inconsistencies in descriptions of AEs and criteria for grading severity, this approach may lead to problems with identification of events due to worsening conditions, differential grading among study sites, tracking event evolution over time, and enumeration of unique events. To address these issues, upcoming clinical trials conducted under the Autoimmunity Centers of Excellence (sponsored by NIH/NIAID/DAIT) will pilot an approach for categorizing and grading AEs at the study site during the data collection phase using a well-defined ontology. Site investigators will be trained to categorize and grade all observed signs, symptoms, and diagnoses (S/S/D) using the Common Terminology Criteria for Adverse Events (Version 3.0) developed by the National Cancer Institute (NCI-CTCAE). In addition, investigators will apply the coding scheme to S/S/D identified during screening so that treatment-emergent “new” adverse events may be easily identified and “worsening conditions” may be unambiguously defined. After the screening period, each new or worsening S/S/D will be recorded only once on the AE Case Report Form (CRF) Log and tracked until resolution. Investigators can report increases in severity using data correction forms so that the highest severity grade for each event will be captured in the database. Investigators will describe events using a clinical diagnosis, if available, and grade the event based on the worst symptom. In the absence of a diagnosis, events will be described using “AE terms” from the NCI-CTCAE system and graded accordingly.

The proposed poster will illustrate the need for reporting standards, detail advantages of the planned approach, and report on experiences from the first months after implementation.
P 144
IMPACT OF NEW EXTERNAL RESEARCH RESULTS IN AN ONGOING CLINICAL TRIAL
Amy K. Darke, Jo Ann L. Hartline and Phyllis J. Goodman
Southwest Oncology Group Seattle, Washington, USA

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) is a randomized double blind trial that examines whether selenium and vitamin E alone or in combination can decrease prostate cancer incidence. SELECT opened in 2001 and is conducted at 427 sites in the US, Canada, and Puerto Rico. 35,534 men were randomized; all men will be followed for at least seven years.

Antioxidants such as selenium and vitamin E are an area of current research interest in a number of health areas. The initial challenge in SELECT was requesting participants to give up their selenium and vitamin E; in particular, vitamin E was commonly believed to improve heart health. Since SELECT opened, several articles have been published about risks associated with vitamin E and/or selenium. In a secondary analysis, selenium was found to increase basal and squamous cell skin cancers. A meta-analysis of vitamin E suggested that high doses may increase the risk of death. Another secondary vitamin E analysis showed an increased risk of congestive heart failure (CHF) among men with a history of CHF, diabetes, or other CHF risk factors. These publications, and the potential for future such publications, have presented unanticipated challenges in study implementation.

Depending on results and the associated media coverage, new research has the potential to change the attitudes of participants and staff, increase drop-in or drop-out rates, require additional data collection or revisions to the study protocol, or require participants be notified and reconsented. Clinical trials must be prepared to respond to positive or negative research results regarding their study agents. We will discuss SELECT’s experience, emphasizing the effects of negative outcomes of external research.

P 145
ADDING NEW SITES TO A MULTINATIONAL TRIAL
Myra A. Carpenter, Andrew Bostom, Alvaro Pacheco-Silva, John Kusek and Lisa Gravens-Mueller
University of North Carolina, Chapel Hill, North Carolina, USA

The Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) trial is evaluating whether homocysteine-lowering vitamin therapy reduces cardiovascular disease (CVD) events in kidney transplant recipients. Enrollment commenced August 2002 at 18 U.S. sites and 2 Canadian sites. Slow recruitment prompted Investigators to increase the number of clinical centers, adding 9 U.S. sites and one Brazilian site. The DSMB approved the expansion but questioned potential event rate incongruity and unknown data reporting quality from the proposed Brazilian site. Other considerations with adding new sites, including a site in Brazil, include participant heterogeneity of clinical care, medical history, competing risks, CVD etiology, compliance, and the uniformity of endpoint ascertainment.

Enrollment of 4,000 participants closes in January 2007. Approximately 75% of participants are from U.S. sites, 12% from Canadian sites, and 13% from Brazil. The study would not have met its recruitment goal without the additional sites, and the Brazilian site enrolled more participants than any other site. Although differences by country in baseline characteristics are evident, the pattern is inconsistent. Statistical methods to adjust for any substantial differences in baseline factors will be used for pooled data.

| Preliminary Baseline Data (percent or mean ± sd) |
|-----------------|-----------------|-----------------|
| Brazil n = 477  | Canada n = 473  | U.S. n = 2,862  |
| Male            | 66%             | 66%             | 62%             |
| Age, years      | 49 ± 8.6        | 53 ± 10.2       | 52 ± 9.3        |
| BMI             | 27 ± 4.6        | 28 ± 6.1        | 30 ± 6.6        |
| Systolic BP     | 146 ± 23.4      | 133 ± 16.8      | 135 ± 18.9      |
| Diastolic BP    | 92 ± 13.7       | 78 ± 9.5        | 76 ± 10.6       |
| History of diabetes | 25%          | 26%             | 43%             |
| Previous MI     | 4%              | 7%              | 9%              |
| Previous stroke | 7%              | 2%              | 6%              |
| Living donor    | 62%             | 37%             | 38%             |
Abstracts 451

P 146
ADHERENCE ASSESSMENT IN THE HOMOCYSTEINE STUDY (HOST), A VA COOPERATIVE STUDY WITH CENTRALIZED FOLLOW-UP AND DIRECT-TO-PATIENT DRUG SHIPMENTS
Stuart R. Warren
Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico, USA

Purpose To compare methods of determining medication adherence in a clinical trial using centralized patient follow-up and drug distribution.

Background HOST is a randomized, placebo-controlled trial involving 2,056 patients to determine if high-dose plasma homocysteine-lowering vitamins reduce mortality and morbidity in patients with kidney disease and high homocysteine levels. Study drug was mailed to patients from a central pharmacy. Follow-up was by telephone or mail. Median follow-up was 3.2 years.

Methods/Results Two measures used to assess medication adherence: 1) patient responses to survey questions regarding missed/extra doses, and 2) capsule counts, were compared by matching quarterly survey responses with capsule counts within the same quarter. Preliminary data revealed that 70.0% of study medication bottles were returned to the central pharmacy. Capsule counts identified more patients who were (i) under-adherent (16.6%) than self-reports did (10.2%), and (ii) over-adherent (7.6%) than self-reports did (0.3%). There was little agreement between the two measures beyond that expected by chance: the Kappa statistic for the overall observed agreement was 0.126. The HOST study recently ended. Final data will be presented.

Conclusion Preliminary data revealed differences in adherence assessed by matching self-reports with capsule counts. This is a conservative analysis that minimizes the chances of finding agreement between the measures. A more clinically relevant approach (in the context of a study of high-dose vitamins with a long duration of action), that compares the measures using an overall per-patient rather than per-bottle analysis and using final data, will also be presented.

P 147
ACADEMIC DETAILING AND HANDHELD TECHNOLOGY: IMPACT ON PROVIDER KNOWLEDGE AND COMFORT
Erica L. Wenzel, David C. Goff, Jr., Patricia Hogan and Denise Bonds
Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA

Adherence to guidelines is low. GLADHeart was a randomized, practice-based trial testing the effects of a personal digital assistant (PDA) decision support tool on adherence to a cholesterol clinical practice guideline (CPG), ATPIII. The experimental group received Academic Detailing (AD) regarding ATPIII and a PDA equipped with a cholesterol management tool. The control group received AD regarding the hypertension CPG (JNC-7) and automated blood pressure devices.

Pre- and post-intervention, providers were surveyed regarding use, comfort and satisfaction with handhelds and technology, and in separate scales, knowledge and comfort using ATPIII and JNC-7. Responses were summed for each scale. Knowledge of both CPGs increased in both the intervention and control group at the end of the study. However, despite limiting education of each group to their assigned guideline there was no difference between groups by guideline assignment. There was a significant difference in attitudes regarding use of technology, favoring the intervention (p = .05), attributable to the PDA tool provided (increase of 1 on 5-point likert scale). A number of factors may account for the lack of between-group differences in CPG scales. Responses to the pre-intervention survey were clustered, indicating a ceiling effect (at least 3 on 5-point scale for 10/12 items). Social confirmation may have contributed. Although the survey was anonymous, physician investigators distributed the survey and were present when providers completed it, potentially influencing responses. Finally, education about any CPG may result in increased comfort and performance of related CPGs. Future studies should consider more sensitive scales with room for change and the impact of social confirmation to understand how education about specific CPG's affects comfort and awareness of other CPG's.

P 148
ASCERTAINING DEMENTIA RELATED OUTCOMES FOR DECEASED OR PROXY-DEPENDENT PARTICIPANTS: AN OVERVIEW OF WHIMS SUPPLEMENTAL CASE ASCERTAINMENT PROTOCOL (SCAP)
Sarah A. Jaramillo, Steve R. Rapp, Pamela D. Nance, Darrin Harris and Debbie Felton
Wake Forest University Health Sciences, Winston-Salem, North Carolina, USA

In clinical trials where the primary endpoint is probable dementia, potential outcomes are missed when participants die or are no longer able to be interviewed. These two groups of individuals represent sub-populations that may be at a greater risk for cognitive impairment and dementia. The Supplemental Case Ascertainment Protocol (SCAP) survey is a standardized, validated instrument to diagnose dementia, principally Alzheimer’s disease, in these particular individuals.
A sub-study of Women’s Health Initiative Memory Study (WHIMS), SCAP, administered this survey by telephone to willing informants identified by the participants as their proxies. 79.6% of the proxies indicated they were willing to complete the SCAP survey. Data entry of the survey was web-based and an algorithm to score the survey was developed by an expert in the field of geriatric psychiatry to classify participants into exclusive categories of normal, mild cognitive impairment, or probable dementia. To validate this algorithm, all surveys were independently classified by a local clinical expert for quality control. When the algorithm successfully returned a diagnosis, 89% of the time it agreed with the quality control diagnosis. 100% of probable dementia diagnoses, half of mild cognitive impairment diagnoses, and 10% of normal diagnoses were sent to two adjudicators. The cases chosen for adjudication and the adjudicators were randomly determined using a programmatic algorithm. Various challenges arose during the implantation of this new protocol including issues related to survey administration, HIPAA concerns, and analytical complexities resulting from two different methods for case determination. Although challenges occurred, SCAP is a feasible protocol and of great potential value.

P 149
CLINICAL VERSUS STATISTICAL SIGNIFICANCE IN THE IRANIAN POSTGRADUATE PERIODONTAL THESES
Surena Vahabi, Robabe Noormohamady and Sahar Rahnama
Tehran, Iran

Background There is too much reliance on using statistical significance testing in clinical trials, that sometimes leads to ignore clinical importance and statistical significance may be assumed as substantively important. According to different concepts and lack of specific clinical criteria in this field, the purpose of this study was to evaluate clinical versus statistical significance in the postgraduate periodontal theses from the first number until the end of 2004 in Iran

Methods All of the experimental periodontal theses in all six postgraduate dental faculties in Iran were evaluated and every direct and indirect evidence of clinical significance were double checked in titles, methods and materials, results, conclusions and suggestions by two trained dental interns. About one- third of the theses were triple checked by the trained director at the end of the study.

Results About 83 percent of accessible experimental theses had statistically significant results and 23.6 percent had some evidence of clinical significance.

Conclusions The results of this study suggest that clinically significant changes related to periodontal therapy should be established and threshold values of each clinical parameters should be defined before at the beginning of the study and then statistical testing can be used to validate that findings did not occur by chance.

Key words: Statistical Significance, Clinical Significance, Periodontal Therapy, Clinical Trial

P 150
CLINICAL AND STATISTICAL SIGNIFICANCE IN NON-INFERIORITY MEDICAL DEVICE TRIALS
Lakshmi Vishnuvajjala, Lakshmi
U.S. Food and Drug Administration Rockville, Maryland, USA

In medical device trials, non-inferiority trials are quite common. In spite of sophisticated trial designs for establishing either superiority and if it fails non-inferiority in the same trial, and variable margins for the difference, it is still common to see submissions where only statistical significance is emphasized without any regard to clinical significance. This is particularly an issue for class II medical devices, which are regulated by requiring that the new device be substantially equivalent to the predicate device. Unless clinical significance is carefully considered, and often even when it is considered, there is a danger of a device which is not safe and effective being substantially equivalent to one that is already on the market. We will provide examples of cases where this could happen and methodologies to guard against it.

P 151
COMPARATIVE EVALUATION OF BALANCING PROPERTIES OF STRATIFIED RANDOMIZATION PROCEDURES
Guenther Kundt
University of Rostock, Rostock, Germany

In any clinical trial there are prognostic factors of interest besides the treatment effect. Some factors are known in advance to be associated with the outcome of a patient. It is often recommend that the randomization for a clinical trial should be stratified on these factors, particularly in a multi-center trial. Unfortunately, stratified or covariate-adaptive randomization do not always promote greater balance between the numbers of treatment assignments to group A and group B within each stratum and thus overall. Because such designs have numerous parameters that must be specified simulation is a good tool to investigate the impact of theses parameters to balance. We investigated and discussed in more detail the difference in balancing performance of three stratified randomization procedures. The permuted-block randomization within strata (1), the method of “minimization” by Pocock and Simon (2) and the “self-adjusting” design by Nordle and Branmark (3) are assessed overall, within levels of prognostic factors, and within strata. We show the superior performance of “self-adjusting” design and the extent of balancing losses occurring by the permuted-block randomization within levels of factors and by the
“minimization” within strata. Finally, a summary of principal conclusions regarding the balancing properties of stratified randomization procedures is presented and general recommendations are offered.

References:

P 152
CONTINGENCY PLANNING IN THE DESIGN OF LONG-TERM CLINICAL TRIALS
Jamie Barnhill, Dianne Peterson, David Garnand and Mike Sather
VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC)
Albuquerque, New Mexico, USA

The design of long-term clinical trials involves many more planning issues than the design of short-term trials. Although the definition of ‘long-term’ may differ depending on the therapeutic plan, the disease under study or the scientific question, all long-term trials share in common the need for additional planning. The VA Cooperative Studies Program CRPCC has extensive background and experience in contingency planning for long-term clinical trials.

The purpose of this report is to describe and outline the important contingency planning aspects of long-term clinical trial design. Contingency planning addresses changes and potential problems that are predictable occurrences when studies are carried out over long periods of time. These design considerations include diagnostic and analytical technology changes that can effect subject recruitment, software and hardware obsolescence that can effect data collection, subject attrition, alterations in drug supply chains, clinical sample storage and retrieval, regulatory changes, and human resource issues, such as investigator age, and the continuing education, cross-training and retirement of study personnel. Examples, both from experience and from the literature, will highlight the importance of these aspects to the study data, as well as to the completion of the clinical trial. The proper design of a long-term clinical trial must take into consideration these additional issues to insure that after all of the years of a long study, following extensive hard work and many dollars spent, the scientific question can be answered.

P 153
INTEGRATING EMERGENCY MANAGEMENT INTO CLINICAL TRIALS STUDY DESIGN
Dianne E. Peterson, David Garnand and Jamie Barnhill
VA Cooperative Studies Program,
Albuquerque, New Mexico, USA

Disasters, whether natural or manmade, can devastate a clinical trial costing time, money, scientific data, and the health and welfare of study subjects. Emergency preparedness is a cycle of mitigation, preparedness, response, and recovery that should be an essential part of clinical trial planning. A written, tested and approved Emergency Management Process Plan (EMPP), along with trained teams, can aid study staff during a disaster.

The purpose of this presentation is to describe a proposed model for integrating a clinical EMPP into the design of a trial using the CRPCC Clinical Trials Project Plan (CTPP) template. This template addresses all phases of study operation, from study planning through to close out.

The EMPP would be incorporated into the planning phase of the project plan following a vulnerability analysis, which must address the potential impact of a variety of disasters on all aspects of the clinical trial, for example, the type of study, the drug supply chain, the anticipated subject demographics, and the location of study sites. Economic issues would be addressed at the funding phase of design based on the vulnerability analysis. Emergency preparedness training is then performed during the kickoff. Emergency drugs/devices need to be delivered to sites during all active phases of the trial, with monitoring and stock rotation. An effective communications plan, essential to the success of the EMPP, will be aided by the use of a specialized web application. It is the responsibility of all study partners to ensure the safety of study subjects, as well the survival and integrity of a trial. A proactive, planned, tested, and continuously updated EMPP would assure these goals are met.

P 154
CHALLENGES FACED AND SOLUTIONS IMPLEMENTED BY A DATA COORDINATING CENTER FOR A SINGLE SITE AND MULTISITE HEALTH RESEARCH NETWORK IN DEVELOPING COUNTRIES
Hrishikesh Chakraborty
RTI International Cary, North Carolina, USA

Data Coordinating Centers (DCC) for clinical trials typically assist clinical investigators and their research team by helping develop trial materials, providing leadership on statistical design and analyses approaches, developing

http://ctj.sagepub.com

Clinical Trials 2007; 4: 371–455
data collection and management systems, coordinating study communication and logistics, training project staff, ensuring data quality, analyzing data, and preparing manuscripts. DCCs for international multi-country and multisite clinical trials face a unique set of challenges beyond those presented by domestic single or multisite clinical trials due to differences in language and culture, time zones, technology, communication style, and project staff training.

In this paper we describe innovative strategies for coordinating single site and multisite international clinical trials in developing countries that have not previously been described in literature. As an example this paper illustrates challenges faced by the Global Network (GN) for Women's and Children's Health Research, an international health research network that conducts single site and multisite clinical trials in developing countries. Challenges and solutions will be presented for the topics of key staff training, IT infrastructure, ethical reviews, materials development, translations, data management systems, data quality assurance, statistical challenges, training and material procurement.

This work was funded through grants from the National Institute of Child Health and Human Development (NICHD) U01 HD40636 and the Bill and Melinda Gates Foundation.

P 155
TRAINING PROGRAMS FOR CLINICAL TRIAL PERSONNEL IN GERMANY
Johannes Haerting
University of Halle-Wittenberg, Halle (Saale), Germany

The German Network of Coordinating Centers for Clinical Trials (KKS-N) is a publicly funded Consortium of Clinical Trials Centers at Medical Faculties throughout Germany which consists actually of 14 Centers and further associated units. Besides the central task to perform scientifically high quality and investigator initiated clinical trials the cooperation structure of the network is organized in various working groups, e.g. working groups for quality management, biostatistics and data management. The working group of continuous education and professional training started its activity at the beginning of the network in 1998. It is a central task of the network to enhance and harmonize professional prerequisites and course curricula. Course programs and course curricula have been established for a study nurse training program, an investigator (physician) course, a principal investigator course and an introductory course for clinical monitoring personal. Within the course programs 1.100 study nurses (in 40 courses) and 1.170 trial physicians (in 47 courses) were trained from 1999 to 2006. For the given courses the network awards a unified certificate to the participants. The existing courses were further adapted to different clinical subareas and trial fields (e.g. oncology, pediatrics, surgery, trials for medical products). The network courses are performed not only at the KKS-N locations but also at other universities and places in Germany and in Austria and Switzerland.

The working group is now under way to develop a harmonized curriculum for a master program in clinical research. Some German Universities will develop master programs which will partly be founded by the federal government within its program of clinical trial centers. Patient-oriented clinical research depends on qualified trial personnel. The network courses contribute substantially to highly qualified staff in the trial centers in Germany.

P 156
THE MAX STUDY: MAXIMISING A CLINICAL TRIAL
Victoria Tunney
University of Sydney, Sydney, Australia

Broad topic category of presentation Electronic capture of tissue banking data associated with Oncology clinical trials in the Asia Pacific region.

Topics: Current gastro-intestinal cancer trials in the Asia Pacific region New web based data capture systems The legal and ethical issues of tissue banking in Australia, New Zealand and the United Kingdom

Description: The Australasian Gastro-Intestinal Trials Group (AGITG) is a cooperative network of over 1000 cancer clinicians and researchers interested in cancers of the gastro-intestinal tract. The AGITG is currently conducting 20 cancer trials and is establishing a comprehensive tissue bank linked to high quality clinical data in partnership with the NHMRC Clinical Trials Centre at the University of Sydney, Australia.

The MAX trial a randomised phase II/III study design to evaluate the role of mitomycin C, Avastin and Xeloda in patients with metastatic colorectal cancer. The primary aim of the MAX study is to determine an optimal regimen with reduced toxicity for older patients with metastatic colorectal cancer and patients with associated co-morbidities. Patients otherwise considered for 5-fluorouracil monotherapy will be randomised to capecitabine, capecitabine plus bevacizumab or the combination of capecitabine, bevacizumab and mitomycin C.

The MAX study will be used as an example to highlight the excellent recruitment rates to clinical trials and tissue banking; the new and innovative web-based data capture system designed by the NHMRC Clinical Trials Centre; and address processes required to comply with ethical and legal tissue banking obligations in Australia, New Zealand and the United Kingdom.
MANAGEMENT, GOVERNANCE AND FINANCIAL PRACTICES OF RESEARCH NETWORKS: RESULTS OF THE INVENTORY AND EVALUATION OF CLINICAL RESEARCH NETWORKS (IECRN) PROJECT

Nancy Dianis and Steve Durako
Westat, Rockville, Maryland, USA

A goal of the Inventory and Evaluation of Clinical Research Networks (IECRN) project, which seeks to enhance the efficiency and productivity of clinical research, was to prepare a detailed description of existing clinical research network (CRN) practices from a sample of identified CRNs. Descriptive Surveys were conducted with members of a sub sample of CRNs to gather detailed information about the practices that each CRN employs to organize and conduct research.

Key findings from two of the survey modules will be presented. The Management and Governance instrument addressed the research focus of the network, staff composition; policies, procedures, and practices related to creation and dissemination of findings; and policies and practices relating to scientific productivity. The instrument also assessed presence and content of bylaws and standard operating procedures; organizational roles and functions; decision-making processes; establishing the scientific agenda; leadership; policymaking and evaluation. The Financial Practices instrument asked about funding issues, policies and practices; current sources and types of network funding; fundraising efforts; cost structure and coverage, cost accounting and accountability; and challenges of and responses to managing funds to accomplish the network’s goals and objectives.

The presentation of these data seeks to foster collaboration, facilitate information and practice sharing among networks, and to stimulate the discussion of possible best practices for clinical research networks. The IECRN is funded by the National Institutes of Health (NIH) and led by the National Center for Research Resources, a component of NIH. It stems from the NIH’s commitment to re-engineer the clinical research enterprise, one of the key objectives of the NIH Roadmap for Medical Research.